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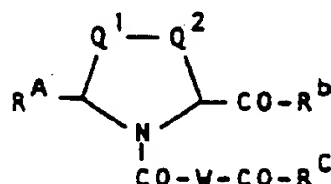
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54 Thiazolidine and pyrrolidine compounds, processes for their preparation and pharmaceutical compositions containing them.

57 Thiazolidine and pyrrolidine compounds which have the general formula



and salts thereof for preventing or relieving diabetic complications and for reducing blood pressure, the processes for their preparation, and the compositions comprising them and pharmaceutically acceptable excipient(s).

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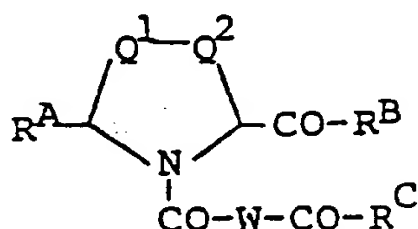
TITLE OF INVENTION

THIAZOLIDINE AND PYRROLIDINE COMPOUNDS, PROCESSES FOR THEIR
 PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING
 5 THEM

BACKGROUND OF INVENTION

10

This invention relates to thiazolidine and pyrrolidine
 compounds of the general formula



[I],

15

wherein

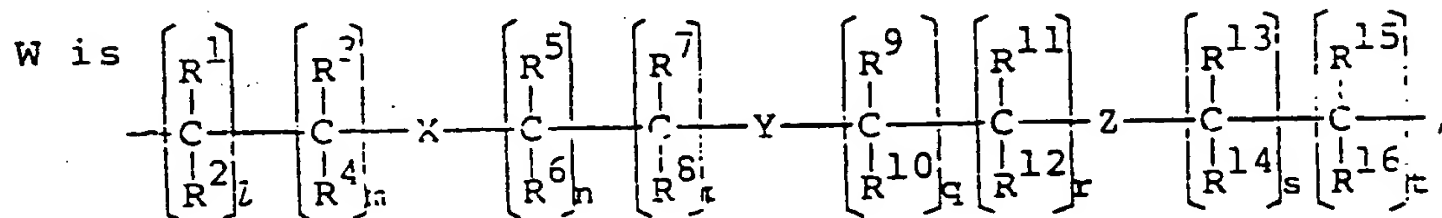
Q^1 and Q^2 each is methylene or sulfur, but Q^1 and Q^2
 are not sulfur at the same time;

20

R^{A} is R^{a} or R^{b} ;

R^{B} and R^{C} each is R^{c} ;

25



X, Y and Z each is single bond, $-\text{CH}_2-$, $-\text{C}(\text{R}^{17})=\text{C}(\text{R}^{18})-$, $-\text{C}\equiv\text{C}-$, $-\text{C}(\text{R})=\text{C}(\text{R})-$

1 -O-, -CO-, -S-, -SO-, -SO₂-, $\begin{array}{c} \text{C} \\ \parallel \\ \text{N}-\text{R}^{20} \end{array}$, -NHCONH-, $\begin{array}{c} \text{N} \\ \diagup \quad \diagdown \\ \text{N} \end{array}$ or $\begin{array}{c} \text{N} \\ | \\ \text{R}^{21} \end{array}$;

l, m, n, p, q, r, s and t each is 0, 1, 2 or 3;
 R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴,
 R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰ and R²¹ each is R^d;

5 R^A is R^b when W is $\begin{array}{c} \text{R}^{23} \\ | \\ \text{CH}-\text{NH}-\text{C}- \\ | \quad | \\ \text{R}^{22} \quad \text{R}^{24} \end{array}$ or $\begin{array}{c} \text{CH}-(\text{CH})_{0-2} \\ | \quad | \\ \text{R}^{25} \quad \text{R}^{26} \end{array}$, wherein
 R²², R²³, R²⁴, R²⁵ and R²⁶ each is R^d;

R^a is selected from the group consisting of
 (i) hydrogen, lower alkyl and lower alkenyl, and
 0 (ii) lower alkyl and lower alkenyl substituted by at least
 one substituent selected from the group consisting of
 lower alkyl, lower alkenyl, hydroxy, lower alkoxy, halogeno-
 lower alkoxy, acyloxy, halogen, nitro, cyano, amino, lower
 alkylamino, dialkylamino, acylamino, mercapto, acylmercapto,
 lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxy-
 carbonyl, aryloxycarbonyl, sulfamoyl, lower alkylamino-
 5 sulfonyl and lower alkylsulfinyl;

R^b is selected from the group consisting of
 (a) (i) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl, and
 (ii) aralkyl, heteroalkyl, aralkenyl and heteroaralkenyl
 substituted by at least one substituent selected from the
 group consisting of lower alkyl, lower alkenyl, halogeno-
 lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy,
 acyloxy, halogen, nitro, cyano, amino, lower alkylamino,
 dialkylamino, acylamino, mercapto acylmercapto, lower
 alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxy-
 carbonyl, aryloxycarbonyl, sulfamoyl, lower alkylamino-
 sulfonyl and lower alkylsulfinyl, and
 5 (iii) carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl,

1 aryloxycarbonyl and heteroaryloxycarbonyl;

(b) (i) phenyl and naphthyl, and

(ii) phenyl and naphthyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, aralkyloxy, aryloxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxy-carbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

(c) (i) furyl, thienyl and pyridyl, and

(ii) furyl, thienyl and pyridyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, aralkyloxy, aryloxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxy-carbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

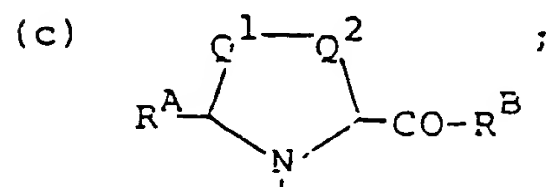
R^C is selected from the group consisting of

(a) (i) hydroxy, lower alkoxy and amino, and

(ii) lower alkoxy, and amino substituted by at least one substituent selected from the group consisting of lower alkyl, aralkyl, heteroaralkyl, aralkenyl, heteroaralkenyl, hydroxy, lower alkoxy, aralkyloxy, heteroaralkyloxy, aryloxy, hetero-aryloxy, acyloxy, aryl, heteroaryl, substituted aralkyl and substituted aryl wherein the substituent is lower alkyl, lower alkoxy, halogen or amino;

(b) (i) aryloxy and heteroaryloxy, and

(ii) aryloxy and heteroaryloxy substituted by at least one substituent selected from the group consisting of lower alkyl, hydroxy, lower alkoxy, halogen and amino, and



1 R^d is selected from the group consisting of
(a) (i) hydrogen, lower alkyl, lower alkenyl, aralkyl, hetero-
aralkyl, alkanoyl, arylalkanoyl, heteroarylalkanoyl, hydroxy,
carboxy, amino, mercapto and sulfo, and
(ii) lower alkyl, lower alkenyl, aralkyl, heteroaralkyl,
5 alkanoyl, arylalkanoyl, heteroarylalkanoyl, hydroxy, carboxy,
amino, mercapto and sulfo substituted by at least one substituent
selected from the group consisting of lower alkyl, lower alkenyl,
lower alkoxy, lower alkanoyl, aryl, heteroaryl, acyloxy, aroyl,
hydroxy, carboxy, amino, guanidino, mercapto, acylamino,
acylmercapto, lower alkoxycarbonyl, sulfo, halogen, nitro,
cyano, sulfamoyl, lower alkylaminosulfonyl, lower alkylthio
10 and lower alkylsulfinyl;

(b) (i) phenyl and naphthyl, and
(ii) phenyl and naphthyl substituted by at least one substituent
selected from the group consisting of lower alkyl, lower alkoxy,
lower alkanoyl, acyloxy, hydroxy, carboxy, amino, halogen,
nitro, cyano, acylamino, mercapto, acylmercapto, halogeno-
15 lower alkyl, halogeno-lower alkoxy, lower alkylenedioxy, lower
alkoxycarbonyl, sulfo, sulfamoyl, lower alkylaminosulfonyl
and lower alkylsulfinyl;

(c) (i) furyl, thienyl and pyridyl, and
(ii) furyl, thienyl and pyridyl substituted by at least one
substituent selected from the group consisting of lower alkyl,
lower alkoxy, lower alkanoyl, acyloxy, hydroxy, carboxy, amino,
20 halogen, nitro, cyano, acylamino, mercapto, acylmercapto,
halogeno-lower alkyl, halogeno-lower alkoxy, lower alkylene-
dioxy, lower alkoxycarbonyl, sulfo, sulfamoyl, lower alkyl-
aminosulfonyl and lower alkylsulfinyl;

and salts thereof which are useful as agents for therapy or
25 prophylaxis of the diabetic complication because they inhibit
strongly aldose reductase, and as antihypertensive agents
because they inhibit angiotensin I-converting enzyme.

1. The compounds [I] of this invention can be prepared by following process.

(i) A compound of the formula [I] is yielded by the reaction of a compound of the formula [II]



10 wherein R^{A} and R^{B} may be protected by any suitable groups (e.g., lower alkyl, acyl, aralkyl, aralkyloxy, etc.) when R^{A} and R^{B} include reactive groups (e.g., amino, hydroxy, mercapto, hydroxyamino, etc.), with the reactive derivative of carboxylic acid of the formula [III] (e.g., acyl halide, acid anhydride, mixed anhydride, active ester, lactone, etc.)
 15 by general methods used in peptide syntheses or amide formation reactions



20 wherein W and R^{C} may be protected by any suitable groups (e.g., lower alkyl, acyl, aralkyl, aralkyloxy, etc.) when W and R^{C} include reactive groups (e.g., amino, hydroxy, mercapto, hydroxyamino, etc.), followed by removal of protective groups by well-known methods (e.g., hydrolysis, hydrogenolysis, ammonolysis, alcoholysis, etc.).
 25

This procedures of deprotection can be applied in the following methods.

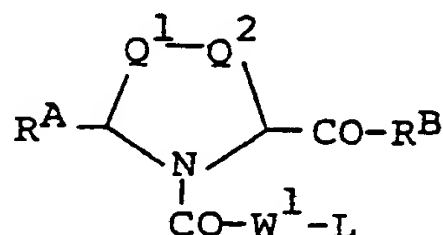
(ii) A compound of the formula [I] is yielded by the reaction of a compound of the formula [II] with the reactive derivative of carboxylic acid of [IV] (e.g., above-mentioned)



[IV],

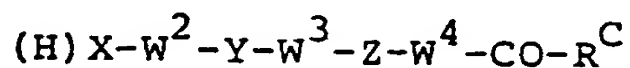
wherein W^1 is $\begin{bmatrix} R^1 \\ | \\ -C- \\ | \\ R^2 \end{bmatrix}_l \begin{bmatrix} R^3 \\ | \\ -C- \\ | \\ R^4 \end{bmatrix}_m$, and may be protected such as (i)

above, L is a leaving group (e.g., halogen, alkylsulfonyl, arylsulfonyl, etc.), by the same methods as described in (i) above to produce a compound of the formula [V]



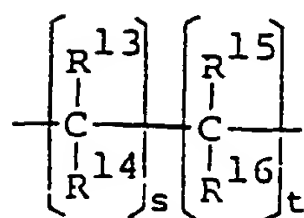
[V]

and then reaction of a compound of the formula [V] with a compound of the formula [VI]



[VI],

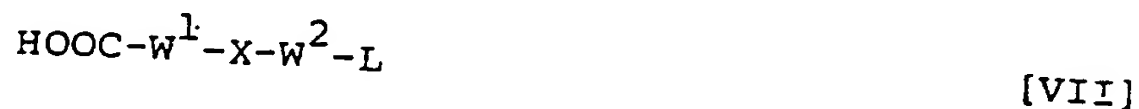
wherein W^2 is $\begin{bmatrix} R^5 \\ | \\ -C- \\ | \\ R^6 \end{bmatrix}_n \begin{bmatrix} R^7 \\ | \\ -C- \\ | \\ R^8 \end{bmatrix}_p$, W^3 is $\begin{bmatrix} R^9 \\ | \\ -C- \\ | \\ R^{10} \end{bmatrix}_q \begin{bmatrix} R^{11} \\ | \\ -C- \\ | \\ R^{12} \end{bmatrix}_r$, W^4 is



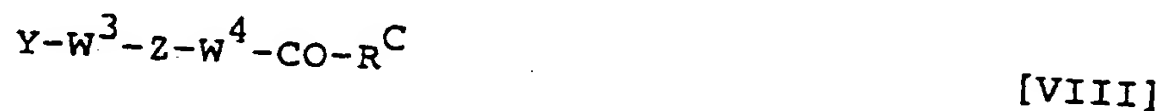
, and W^2 , W^3 , W^4 , X, Y, Z and R^C may be

1⁶ protected such as (i) above, in the presence of proper alkaline and/or organic bases, if necessary, by known methods.

5 (iii) A compound of the formula [I] is yielded by the reaction of a compound of the formula [II] with the reactive derivative of carboxylic acid of the formula [VII] (e.g., mentioned in (i) above)

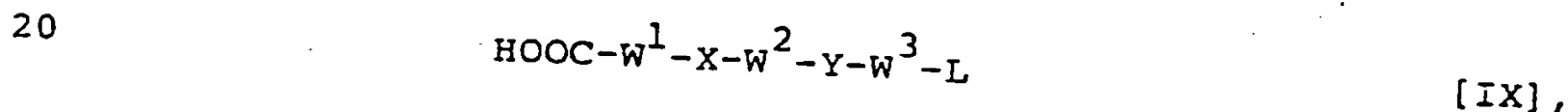


10 and then with a compound of the formula (VIII)

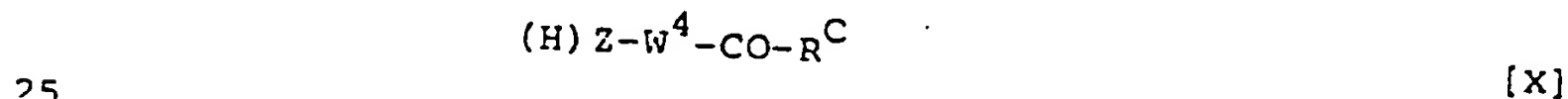


by the same method as (ii) above.

15 (iv) A compound of the formula [I] is yielded by the reaction of a compound of the formula [II] with the reactive derivative of carboxylic acid of the formula [IX] (e.g., mentioned in (i) above)



and then with a compound of the formula [X]



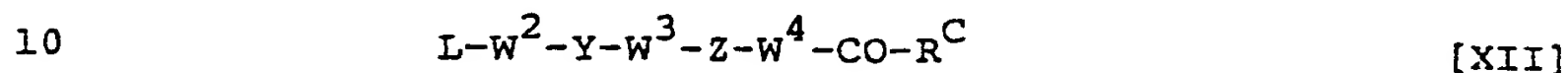
by the same method as (ii) above.

9

1 (v) A compound of the formula [I] is yielded by the reaction of a compound of the formula [II] with the reactive derivative of carboxylic acid [XI] (e.g., acyl halide, acid anhydride, mixed anhydride, active ester, lactone, thiolactone, etc.)

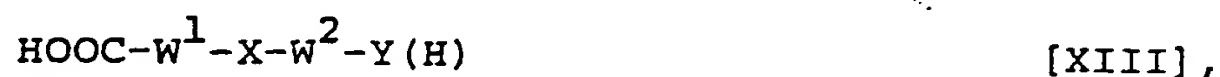


and then with a compound of the formula [XII]



by the same method as (ii) above.

(vi) A compound of the formula [I] is yielded by the reaction of a compound of the formula [II] with the reactive derivative of carboxylic acid of the formula [XIII] (e.g., mentioned in (v) above)



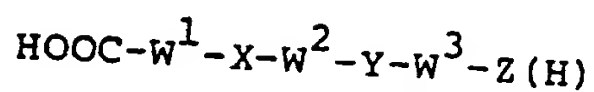
20 and then with a compound of the formula [XIV]



by the same method as (ii) above.

25 (vii) A compound of the formula [I] is yielded by the reaction of a compound of the formula [II] with the

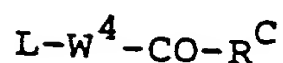
- 1 reactive derivative of carboxylic acid of the formula [XV]
(e.g., mentioned in (v) above)



[XV],

5

and then with a compound of the formula [XVI]



[XVI]

- 10 by the same method as (ii) above.

(viii) A compound of the formula [I] is also yielded by converting a compound of the formula [I] prepared by any method above-mentioned by well-known methods (e.g., oxidation, formation of oxime, hydrazone and semicarbazone, addition to double bond, etc.)

15

The compounds [I] of this invention are effective on preventing or relieving diabetic complications.

20 In diabetic patients, high levels of hexoses (e.g., glucose, galactose, etc.) in blood lead to the accumulation of sugar alcohols (e.g., sorbitol, galactitol, etc.) in tissues. It is known that this accumulation causes the swelling of cells to induce complications of diabetic cataract, diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, etc. [R. Quan-Ma et al., Biochem. Biophys. Res. Comm., 22, 492 (1966)]. For example, R. Gitzelman et al.

25

1 have presented that cataract is caused by the accumulation
of sugar alcohols [Exptl. Eye. Res., 6, 1 (1967)]. A report
of Kinoshita et al. has demonstrated that aldose reductase
which reduced aldose to the corresponding sugar alcohols
5 was involved in the initiation of these diabetic
complications and that effective inhibitors of aldose
reductase were useful [Jpn. J. Ophthalmol., 20, 339 (1976)].
On the basis of the above information, aldose reductase
inhibition of the compounds [I] of this invention was tested.
10 The results of the examinations demonstrated that these
compounds have potent inhibitory activities on aldose
reductase, and therefore they are useful as drugs for therapy
or prophylaxis of the diabetic complications.

On the other hand, it has been known that a kind of the
15 derivatives of thiazolidine- or pyrrolidinecarboxylic acid
have potent inhibitory activity to angiotensin I-converting
enzyme, but thiazolidine and pyrrolidine compounds of this
invention are novel compounds, and have more potent inhibitory
activities to angiotensin I-converting enzyme. Furthermore,
20 the compounds of this invention are prepared by convenient
methods, and are superior to the stability.

Thus, the compounds of this invention are useful as
therapeutic or prophylactic agents and antihypertensive
agents.

25

The compound of formula [I] can form the conventional

1 salts to be generally used as medicine such as sodium salt,
potassium salt, calcium salt, magnesium salt, aluminum salt,
ammonium salt, diethylamine salt, triethanolamine, etc.

5 The compounds of formula [I] have the stereoisomers
which are within the limit of this invention, because they
have one or more asymmetric carbon atoms.

Typical examples are shown below, although this invention
is not limited to these examples.

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EXAMPLE 1

(4R)-3-(7-Carboxyheptanoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid (compound 20)

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(4R)-2-(2-Hydroxyphenyl)-4-thiazolidinecarboxylic acid (6.8g,) in N sodium hydroxide (30ml) and octanedioyl dichloride (6.3g,) were added dropwise to 1M potassium carbonate (60ml) with stirring under ice-cooling. After the addition, the reaction mixture was stirred for 1 hour at the same temperature and for additional 1 hour at room temperature. The solution was acidified with dilute hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residual oil^{*2} was purified by silica gel column chromatography to give 7.0g (61%) of the titled compound: mp 155-157°C (dec.) (ethyl acetate); $[\alpha]_D^{27} +134.1^\circ$ (c=0.5, methanol). IR (nujol, cm^{-1}): 3220 (OH), 1710 (COOH), 1620 (CON), 1600 (aromatic), 1415, 1235, 1172, 950, 760. NMR (DMSO- d_6 , δ): 0.53-1.73 (8H, m, $-\text{CH}_2(\text{CH}_2)_4\text{CH}_2-$) 1.77-2.57 (4H, m, $-\text{CH}_2(\text{CH}_2)_4\text{CH}_2-$), 3.03 (1H, AB_q (A part), d, J=11.5, 8.5Hz, C₅^{*1}-H_A), 3.37 (1H, AB_q (B part), d, J=11.5, 6.5Hz, C₅-H_B), 4.60 (1H, dd, J=8.5, 6.5Hz, C₄-H), 6.28 (1H, s, C₂-H), 6.45-8.07 (4H, m, arom. H), 9.77 (1H, s, -COOH). TLC: Rf value^{*3} 0.52.

*1 The numbers represent the positions on thiazolidine or

- 1 pyrrolidine ring. The same shall be applied hereinaft
- *2 Two spots were observed on the TLC (ethyl acetate-
chloroform-acetic acid (10:5:3)), and two products
could be separated by silica gel column chromatography
- 5 From NMR spectra, the upper and lower spots were
identified as the titled compound and (4R,4R')-3,3'-
(octanedioyl)bis[2-(2-hydroxyphenyl)-4-thiazolidine-
carboxylic acid] (compound 40), respectively.
- *3 Silica gel, ethyl acetate-chloroform-acetic acid
10 (10:5:3).

The compounds shown in Table I and III were prepared by
the same procedure as described above.

The following compounds are also prepared by the same
15 procedure as EXAMPLE 1.

- (4R)-3-carboxyacetyl-4-thiazolidinecarboxylic acid
- (4R)-3-(3-carboxypropanoyl)-2-phenyl-4-thiazolidine-
carboxylic acid
- (4R)-3-[3-(2-carboxyethylsulfinyl)propanoyl]-2-(2-
20 hydroxyphenyl)-4-thiazolidinecarboxylic acid
- (4R)-3-[[[2-(carboxymethyloxy)ethyl]oxy]acetyl]-2-(2-
hydroxyphenyl)-4-thiazolidinecarboxylic acid
- (4R)-3-(4-carboxybutanoyl)-2-(3-hydroxyphenyl)-4-
thiazolidinecarboxylic acid
- 25 (4R)-3-(5-carboxypentanoyl)-2-(4-methylphenyl)-4-
thiazolidinecarboxylic acid

- 1 (4R)-3-(6-carboxyhexanoyl)-2-(4-chlorophenyl)-4-thiazolidinecarboxylic acid
- (4R)-3-(7-carboxyheptanoyl)-2-(4-methoxyphenyl)-4-thiazolidinecarboxylic acid
- 5 (4R)-3-(13-carboxytridecanoyl)-2-(2-nitrophenyl)-4-thiazolidinecarboxylic acid
- (4R)-3-(7-carboxyheptanoyl)-2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid
- (4R)-3-[3-(2-carboxyethylthio)propanoyl]-2-(5-nitrophenyl)-4-thiazolidinecarboxylic acid
- 10 (4R)-3-[[[2-(carboxymethyloxy)ethyl]oxy]acetyl]-2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid
- (4R)-3-(6-carboxyhexanoyl)-2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid
- 15 (4R)-3-(9-carboxynonanoyl)-2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid
- (4R)-3-(11-carboxyundecanoyl)-2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid
- (4R)-3-[4-(3-carboxypropyloxy)butanoyl]-2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid
- 20 (4R)-3-[3-(2-carboxyethylsulfonyl)propanoyl]-2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid
- (4R)-3-(9-carboxynonanoyl)-2-(5-chloro-2-hydroxyphenyl)-4-thiazolidinecarboxylic acid
- 25 (4R)-3-(11-carboxyundecanoyl)-2-(3,4,5-trimethoxyphenyl)-4-thiazolidinecarboxylic acid
- (4R)-3-(13-carboxytridecanoyl)-2-(2-acetoxyphenyl)-4-

- 1 thiazolidinecarboxylic acid
(4R)-3-(6-carboxyhexanoyl)-2-(2-furyl)-4-thiazolidine-
carboxylic acid
(4R)-3-(7-carboxyheptanoyl)-2-(2-thienyl)-4-thiazolidine-
5 carboxylic acid
(4R)-3-(8-carboxyoctanoyl)-2-(3-pyridyl)-4-thiazolidine-
carboxylic acid
(4R)-3-(9-carboxynonanoyl)-2-(1-naphthyl)-4-thiazolidine-
carboxylic acid
10 (4R)-3-(5-carboxypentanoyl)-2-(2-hydroxy-4-sulfamoyl-
phenyl)-4-thiazolidinecarboxylic acid
(4R)-3-(6-carboxyhexanoyl)-2-(3-cyanophenyl)-4-
thiazolidinecarboxylic acid
(4R)-3-(7-carboxyheptanoyl)-2-(3-difluoromethoxyphenyl)-
15 4-thiazolidinecarboxylic acid
(4R)-3-(8-carboxyoctanoyl)-2-(4-carboxyphenyl)-4-
thiazolidinecarboxylic acid
(4R)-3-(9-carboxynonanoyl)-2-(3-methylsulfinylphenyl)-4-
thiazolidinecarboxylic acid
20

EXAMPLE 2

(4R,4'R)-3,3'-(Octanedioyl)bis[2-(2-hydroxyphenyl)-4-
thiazolidinecarboxylic acid (compound 40)

- 25 To a stirred solution of (4R)-2-(2-hydroxyphenyl)-
4-thiazolidinecarboxylic acid (6.8g) in 1M
potassium carbonate (45ml), octanedioyl dichloride (3.2g)

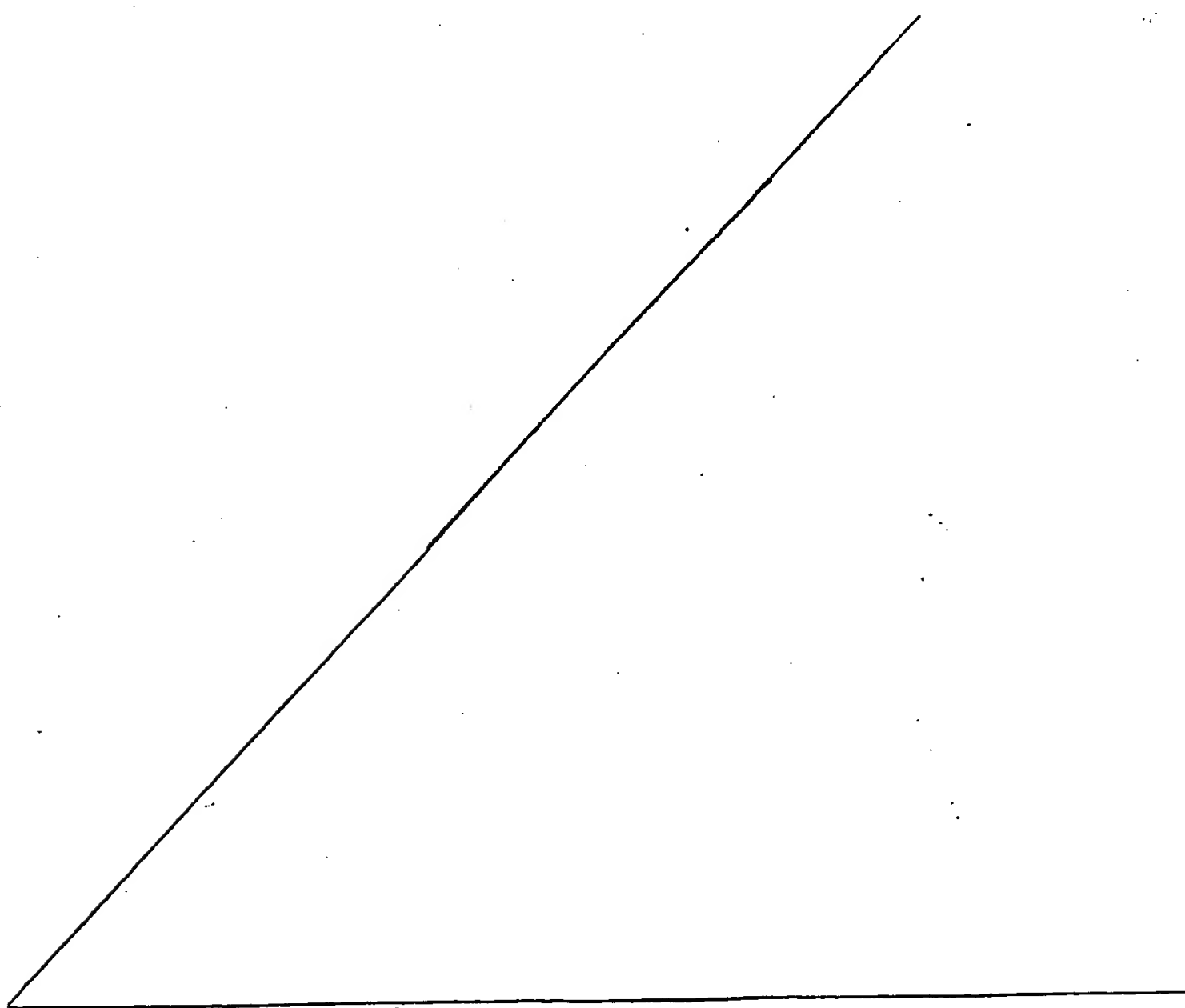
1 was added dropwise under ice-cooling. After the
addition, the reaction mixture was stirred for 1 hour at
the same temperature and for additional 1 hour at room
temperature. The solution was acidified with dilute
5 hydrochloric acid, extracted with ethyl acetate. The

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1 organic layer was washed with saturated sodium chloride
 solution, dried over anhydrous magnesium sulfate, and
 evaporated in vacuo. The residual oil was purified by
 silica gel column chromatography to give 7.6g (86%) of
 5 the titled compound: mp 93-97°C (dec.); $[\alpha]_D^{27} +123.6^\circ$
 (c=0.5, methanol). IR (nujol, cm^{-1}): 1720 (COOH), 1620
 (CON), 1600 (aromatic), 1230, 1090, 855, 765. MNR (CD_3OD)
 10 δ : 0.7-1.7 (8H, m, $-\text{CH}_2(\text{CH}_2)_4\text{CH}_2-$), 1.8-2.4 (4H, m,
 $-\text{CH}_2(\text{CH}_2)_4\text{CH}_2$), 3.25 (4H, d, $J=7.5\text{Hz}$, $\text{C}_5\text{-H}$), 4.81 (2H,
 t, $J=7.5\text{Hz}$, $\text{C}_4\text{-H}$), 6.35 (2H, s, $\text{C}_2\text{-H}$), 6.7-8.0 (8H, m,
 15 arom. H). TLC: Rf value* 0.34.

* Silica gel, ethyl acetate-chloroform-acetic acid
 (10:5:3).

15

The compounds shown in Table II and III were prepared by
 the same procedure as described above.

EXAMPLE 3

20 (4R,4'R)-3,3'-(heptanedioyl)bis[2-(3-cyanophenyl)-4-
 thiazolidinecarboxylic acid] (compound 36)

To a stirred solution of (4R)-2-(3-cyanophenyl)-4-
 thiazolidinecarboxylic acid (4.7g) in 1M sodium
 25 carbonate (30ml), heptanedioyl dichloride (2.1g)
 was added dropwise under ice-cooling. The reaction mixture
 was stirred for 30 minutes at the same temperature, and

1 filtered to give the precipitates. The precipitates were
 dissolved in hot water (100ml), and acidified with
 concentrated hydrochloric acid. The separated crystals
 were collected by filtration to give 3.5g (59%) of the
 5 titled compound: mp 105-112°C; $[\alpha]_D^{25} +115.0^\circ$ (c=1.0,
 methanol). IR (nujol, cm^{-1}): 2270 (CN), 1735 (COOH),
 1640 (CON), 1616 (aromatic), 1195, 790 (aromatic). NMR
 (DMSO- d_6) δ : 0.69-1.66 (6H, m, $-\text{CH}_2(\text{CH}_2)_3\text{CH}_2-$),
 1.70-2.50 (4H, m, $-\text{CH}_2(\text{CH}_2)_3\text{CH}_2-$), 2.85-3.66 (4H, m,
 10 $\text{C}_5\text{-H}$), 4.69 (1H, dd, $J=8.2, 6.0\text{Hz}$, $\text{C}_4\text{-H}$), 5.13 (1H, m,
 $\text{C}_4\text{-H}$), 6.16 (1H, s, $\text{C}_2\text{-H}$), 6.43 (1H, s, $\text{C}_2\text{-H}$), 7.3-8.3
 (8H, m, arom. H). TLC: Rf value* 0.33.

* Silica gel, ethyl acetate-chloroform-acetic acid
 15 (10:5:3).

The compounds shown in Table II were prepared by the
 same procedure as described above.

The following compounds are also prepared by the same
 20 procedure as EXAMPLE 2 or 3.

(4R,4'R)-3,3'-(propanedioyl)bis(4-thiazolidinecarboxylic
 acid)

(4R,4'R)-3,3'-(butanedioyl)bis(2-phenyl)-4-thiazolidine-
 carboxylic acid)

25 (4R,4'R)-3,3'-(3,3'-sulfinyldipropanoyl)bis[2-(2-hydroxy-
 phenyl)-4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-[(ethylenedioxy)diacetyl]bis[2-(2-hydroxy-
 phenyl)-4-thiazolidinecarboxylic acid]

(4R,4'R)-3,3'-[(ethylenedithio)diacetyl]bis[2-(2-hydroxy-
 phenyl)-4-thiazolidinecarboxylic acid]

- 1 (4R,4'R)-3,3'-(pentanedioyl)bis[2-(3-hydroxyphenyl)-4-thiazolidinecarboxylic acid]
(4R,4'R)-3,3'-(hexanedioyl)bis[2-(4-methylphenyl)-4-thiazolidinecarboxylic acid]
- 5 (4R,4'R)-3,3'-(heptanedioyl)bis[2-(4-chlorophenyl)-4-thiazolidinecarboxylic acid]
(4R,4'R)-3,3'-(octanedioyl)bis[2-(4-methoxyphenyl)-4-thiazolidinecarboxylic acid]
(4R,4'R)-3,3'-(tetradecanedioyl)bis[2-(2-nitrophenyl)-4-thiazolidinecarboxylic acid]
- 10 (4R,4'R)-3,3'-(3,3'-thiodipropanoyl)bis[2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid]
(4R,4'R)-3,3'-[(ethylenedioxy)diacetyl]bis[2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid]
- 15 (4R,4'R)-3,3'-(heptanedioyl)bis[2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid]
(4R,4'R)-3,3'-(decanedioyl)bis[2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid]
(4R,4'R)-3,3'-(dodecanedioyl)bis[2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid]
- 20 (4R,4'R)-3,3'-(4,4'-oxydibutanoyl)bis[2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid]
(4R,4'R)-3,3'-(3,3'-sulfonyldipropanoyl)bis[2-(4-nitrophenyl)-4-thiazolidinecarboxylic acid]
- 25 (4R,4'R)-3,3'-(decanedioyl)bis[2-(5-chloro-2-hydroxyphenyl)-4-thiazolidinecarboxylic acid]
(4R,4'R)-3,3'-(dodecanedioyl)bis[2-(3,4,5-trimethoxyphenyl)-4-thiazolidinecarboxylic acid]

- 1 (4R,4'R)-3,3'-(tetradecanedioyl)bis[2-(2-acetoxyphenyl)-4-thiazolidinecarboxylic acid]
(4R,4'R)-3,3'-(heptanedioyl)bis[2-(2-furyl)-4-thiazolidinecarboxylic acid]
- 5 (4R,4'R)-3,3'-(octanedioyl)bis[2-(2-thienyl)-4-thiazolidinecarboxylic acid]
(4R,4'R)-3,3'-(nonanedioyl)bis[2-(3-pyridyl)-4-thiazolidinecarboxylic acid]
(4R,4'R)-3,3'-(decanedioyl)bis[2-(1-naphtyl)-4-thiazolidinecarboxylic acid]
- 10 (4R,4'R)-3,3'-(hexanedioyl)bis[2-(2-hydroxy-5-sulfamoyl-phenyl)-4-thiazolidinecarboxylic acid]
(4R,4'R)-3,3'-(octanedioyl)bis[2-(3-difluoromethoxyphenyl)-4-thiazolidinecarboxylic acid]
- 15 (4R,4'R)-3,3'-(nonanedioyl)bis[2-(4-carboxyphenyl)-4-thiazolidinecarboxylic acid]
(4R,4'R)-3,3'-(decanedioyl)bis[2-(3-methylsulfinyl-phenyl)-4-thiazolidinecarboxylic acid].

20

EXAMPLE 4

(4R,4'R)-3,3'-(Heptanedioyl)bis[2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid] (compound 35)

To a stirred solution of (4R)-2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid (5.1g) in 1M sodium carbonate (40ml), heptanedioyl dichloride (2.1g) was added dropwise under ice-cooling. The

1 reaction mixture was stirred for 1 hour at the same
temperature, and the separated crystals were filtered to
give 4.7g (69%) of the titled compound as disodium salt:
mp 111-113°C (dec.) (water); $[\alpha]_D^{25} +88.2^\circ$ (c=0.5, methanol)
5 IR (nujol, cm^{-1}): 1635 (CON), 1585 (COO^-), 1520 and 1355
(NO_2), 1095, 730. TLC: Rf value* 0.28.

* Silica gel, ethyl acetate-chloroform-acetic acid
(10:5:3).

10

EXAMPLE 5

(4R)-3-(3-Carboxypropanoyl)-2-(2-hydroxyphenyl)-4-
thiazolidinecarboxylic acid (compound 6)

15 To a stirred solution of (4R)-2-(2-hydroxyphenyl)-
4-thiazolidinecarboxylic acid (4.5g) and
triethylamine (4.0g) in acetone (100ml),
succinic anhydride (2.0g) was added at room
temperature, and stirred for 3 hours at the same
20 temperature. The reaction mixture was concentrated
in vacuo, and acidified with dilute hydrochloric acid.
The separated oil was extracted with ethyl acetate, and
the organic layer was washed with saturated sodium chloride
solution, dried over anhydrous magnesium sulfate, and
25 evaporated in vacuo to give 4.9g (75%) of the titled
compound: mp 190-191°C (dec.) (ethyl acetate-methanol);
 $[\alpha]_D^{27} +181.6^\circ$ (c=1.0, methanol). IR (nujol, cm^{-1}): 3210

- 1 (OH), 1720 (COOH), 1618 (CON), 1602 (aromatic), 1245, 1173, 940
763. NMR (DMSO- d_6 , δ): 2.0-2.7 (4H, m, $-\text{CH}_2\text{CH}_2-$), 3.03
(1H, AB_q (A part), d, J=11.0, 10.0Hz, C₅-H_A), 3.36 (1H, AB_q
(B part), d, J=11.0, 7.0Hz, C₅-H_B), 4.61 and 5.07 (1H,
5 dd, J=10.0, 7.0Hz and m, C₄-H), 6.36 (1H, s, C₂-H),
6.5-8.0 (4H, arom. H). TLC: Rf value* 0.35.

* Silica gel, ethyl acetate-chloroform-acetic acid (10:5:3).

- 10 The compounds shown in Table I and III were prepared by the
same procedure as described above. The following compounds
are also prepared by the same procedure as EXAMPLE 5.

(4R)-3-(4-carboxy-4-oxobutanoyl)-2-(2-hydroxyphenyl)-4-
thiazolidinecarboxylic acid

- 15 (4R)-3-(6-carboxy-3,5-dioxohexanoyl)-2-(2-hydroxyphenyl)-
4-thiazolidinecarboxylic acid

(4R)-3-[4-carboxy-3-(methoxyimino)butanoyl]-2-(2-hydroxy-
phenyl)-4-thiazolidinecarboxylic acid.

20 EXAMPLE 6

(4R)-3-[3-(Methoxycarbonyl)-2-methylpropanoyl]-2-(2-
hydroxyphenyl)-4-thiazolidinecarboxylic acid (compound 4)

- To a stirred solution of (4R)-2-(2-hydroxyphenyl)-
25 4-thiazolidinecarboxylic acid (11.3g) in 1M sodium
carbonate (80ml), dl-3-methoxycarbonyl-2-methylpropanoyl
chloride (3.2g) was added dropwise under ice-cooling.

1 After the addition, the reaction mixture was stirred for
1.5 hours at the same temperature. After the filtration
of solution, the filtrate was acidified with dilute
hydrochloric acid, and extracted with ethyl acetate. The
5 organic layer was washed with saturated sodium chloride
solution, dried over anhydrous magnesium sulfate, and
evaporated in vacuo. The residual oil was purified
by silica gel column chromatography to give 7.8g (44%)
of the titled compound: $[\alpha]_D^{25} +161.6^\circ$ (c=1.0, methanol).
10 IR (KBr, cm^{-1}): 3380 (OH), 1723 (COOH, COOCH₃), 1624
(CON), 1235, 1200, 1174, 764.

The compounds shown in Table I and II were prepared by
the same procedure as described above.

15

EXAMPLE 7

(4R)-3-(3-Carboxy-2-methylpropanoyl)-2-(2-hydroxyphenyl)-
4-thiazolidinecarboxylic acid (compound 5)

20 (4R)-3-[3-(Methoxycarbonyl)-2-methylpropanoyl]-2-
(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid (compound
4) (7.1g) was dissolved in 2N sodium hydroxide (40ml)
and stirred for 1 hour at room temperature. The
resulting solution was acidified with dilute hydrochloric
25 acid and the separated crystals were filtered to give
5.1g (75%) of the titled compound: mp 163-164°C (dec.)

1 (ethyl acetate); $[\alpha]_D^{25} +174.1^\circ$ (c=1.0, methanol). IR (nujol, cm^{-1}): 3330 (OH), 1730 and 1710 (COOH), 1629 (CON), 1280, 1234, 856, 771.

5 The compounds shown in Table I and II were prepared by the same procedure as described above. The following compounds are also prepared by the same procedure as EXAMPLE 6 and 7.

10 (4R)-3-[4-(carboxymethyl)benzoyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid

(4R)-3-[(4-carboxyphenyl)acetyl]-2-phenyl-4-thiazolidinecarboxylic acid

(4R)-3-(4-carboxy-3-butenoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid

15 (4R)-3-(4-carboxy-2-butenoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid

(4R)-3-(4-carboxy-3-butyryl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid

20

EXAMPLE 8

(4R)-3-[3-(N-Hydroxycarbamoyl)propanoyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid ethyl ester
(compound 10a)

25

To a stirred solution of (4R)-3-(3-carboxypropanoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid ethyl ester (compound 8a) (1.06g) and N-methylmorpholine (0.33ml)

1 in 20ml of anhydrous tetrahydrofuran, isobutyl chloro-
formate (0.39ml) was added dropwise at -15°C , and stirred
for additional 2 hours at this temperature. To this
solution, the methanol solution of hydroxylamine (0.3g)
5 was added dropwise at -50°C . The reaction mixture was
stirred for 1 hour at room temperature, acidified with
N hydrochloric acid, and extracted
with ethyl acetate. The organic layer was washed with
saturated sodium chloride solution, dried over anhydrous
10 magnesium sulfate, and concentrated in vacuo. The
residual oil was purified by silica gel column chromatography to give 0.7g (63%) of the titled compound. IR
(KBr, cm^{-1}) 3220, 1727, 1625, 1595, 1200, 1092, 753.
NMR (acetone- d_6 , δ): 1.24 (3H, t, $J=7.5\text{Hz}$, $\text{CO}_2\text{CH}_2\text{CH}_3$),
15 2.17-3.07 (4H, m, $\text{CO}-(\text{CH}_2)_2\text{CO}$), 3.30 (1H, AB_q (A part), d,
 $J=10.0$, 2.0Hz , $\text{C}_5\text{-H}_A$), 3.47 (1H, AB_q (B part), d, $J=10.0$,
 7.0Hz , $\text{C}_5\text{-H}_B$), 4.14 (2H, q, $J=7.5\text{Hz}$, CO_2CH_2), 5.18 (1H,
dd, $J=2.0$, 7.0Hz , $\text{C}_4\text{-H}$), 6.40 (1H, s, $\text{C}_2\text{-H}$), 6.88-7.27
(4H, m, arom. H), 8.60 (2H, br. s, NHOH), 9.77 (1H, br. s,
20 OH)

The compounds shown in Table I were prepared by the same
procedure as described above.

25

EXAMPLE 9

(4R,4'R)-3,3'-(Nonanedioyl)bis[2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid methyl ester] (compound 46)

1 To a stirred solution of (4R,4'R)-3,3'-(nonanedioyl)bis-
[2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid]
(compound 47) (3.3g) in ethyl acetate (50ml), 2% ether
5 solution of diazomethane was added dropwise until the
yellow color of diazomethane was not disappeared, and
stirred continuously for 30 minutes. The reaction mixture
was concentrated in vacuo to give 3.3g (96%) of the titled
compound: mp 61-63°C (benzene); $[\alpha]_D^{23} +79.4^\circ$ (c=1.0,
methanol). IR (KBr, cm^{-1}): 1740, 1660, 1530, 1350,
10 1198, 725.

EXAMPLE 10

(4R)-3-[(2-Carboxymethylthio-3-phenyl)propanoyl]-4-
thiazolidinecarboxylic acid (compound 75a and 75b)

15

(4R)-3-[(2-Mercapto-3-phenyl)propanoyl]-4-thiazolidine-
carboxylic acid (1.0g), potassium carbonate (0.7g),
chloroacetic acid (0.2g) and potassium iodide (0.05g)
were dissolved in water (5ml), and stirred for 6 hours
20 at room temperature. The reaction mixture was acidified
with 5N hydrochloric acid and extracted with ethyl acetate.
The organic layer was washed with saturated sodium chloride
solution, dried over anhydrous magnesium sulfate and
concentrated in vacuo. The titled compounds (75a and 75b)
25 were separated from the oily residue by silica gel
column chromatography.

	75a	75b
1		
2	yield 0.4g (37%)	0.5g (47%)
	$[\alpha]_D^{25}$ -52.2° (c=1.2, MeOH)	-60.4° (c=1.0, MeOH)
5	IR 1720, 1620, 1422, (neat, 1217, 756 cm ⁻¹)	1722, 1620, 1420, 1215, 755
10	NMR 2.67-3.63 (6H, m, (CDCl ₃ , δ) -S-CH ₂ -CO ₂ H, C ₅ -H, -CH ₂ -Ph), 3.83-4.83 (3H, m, -CO-CH-S-, C ₂ -H), 4.98 (1H, dd, J=4.5, 6.5Hz, C ₄ -H), 7.22 (5H, s, -C ₆ H ₅) 9.55 (-CO ₂ H)	2.70-3.50 (6H, m, -S-CH ₂ -CO ₂ H, C ₅ -H, -CH ₂ -Ph), 4.00-4.57 (3H, m, -CO-CH-S-, C ₂ -H) 5.02 (1H, dd, J=4.5, 9.5Hz, C ₄ -H), 7.23 (5H, s, -C ₆ H ₅), 10.00 (-CO ₂ H)

15

The compounds shown in Table IV were prepared by the same procedure as described above.

EXAMPLE 11

20 (4R)-3-[(Carboxymethylamino)acetyl]-2-(2-hydroxyphenyl)-
4-thiazolidinecarboxylic acid (compound 81)

25 (4R)-3-Chloroacetyl-2-(2-hydroxyphenyl)-4-thiazolidine-
carboxylic acid (6g) was added to a stirred solution of
glycine (1.5g) in N sodium hydroxide (80ml), and stirred
overnight at room temperature. The solution was adjusted
to pH 1.5 by 20% hydrochloric acid and washed with ethyl
acetate. The aqueous layer was adjusted to pH 3.2, and

1 the separated crystals were collected by filtration to
3.28g (48.2%) of the titled compound: mp 181-182°C (dec.)
(water); $[\alpha]_D^{24} +271.2^\circ$ (c=0.5, MeOH). IR (KBr, cm^{-1}):
3400, 3200, 1740, 1672, 1560, 1440, 1380, 1335, 1212,
5 752, 648, NMR (K_2CO_3 in D_2O , δ): 3.0-4.3 (6H, m, $\text{C}_5\text{-H}$,
 $\text{COCH}_2\text{NHCH}_2\text{CO}_2\text{H}$), 6.33 and 6.43 (1H, each s, $\text{C}_2\text{-H}$), 6.6-
7.3 (3H, m, arom. H), 7.82 (1H, br. d, $J=8\text{Hz}$, arom. H),
9.0-10.3 (2H, br. s, $-\text{OH}$, $-\text{CO}_2\text{H}$).

10 The compounds shown in Table V were prepared by the
same procedure as described above.

EXAMPLE 12

15 (2S)-1-[[(2S)-2-Bis(ethoxycarbonylmethyl)amino]propanoyl]-
2-pyrrolidinecarboxylic acid benzyl ester (compound 88)

Ethyl bromoacetate (0.92g) was added dropwise under
ice-cooling to a stirred solution of L-alanyl-L-proline
benzyl ester p-toluenesulfonate (2.24g) and triethylamine
20 (1.53ml) in dry methylenechloride. After the addition,
the reaction mixture was stirred for 2 hours at room
temperature, refluxed for another 5 hours, and washed with
water and saturated sodium chloride solution. The organic
layer was dried over anhydrous magnesium sulfate and concentrate
25 in vacuo. The residual oil was purified by silica gel column
chromatography to give 1.02g (44.3%) of the titled

- 1 compound: $[\alpha]_D^{24} -67.9^\circ$ ($c=1.2$, MeOH). IR (neat, cm^{-1}): 3460, 1742, 1642, 1428, 1180. NMR (CDCl_3 , δ): 1.23 (6H, t, $J=7\text{Hz}$, $-\text{CO}_2\text{CH}_2\text{CH}_3$), 1.25 (3H, d, $J=7.2\text{Hz}$, $\text{CO}-\underset{\text{CH}_3}{\text{CH}}-\text{N}$), 1.67-
5 2.40 (4H, m, C_3-H and C_4-H), 3.57 (4H, s, $-\text{N}-\text{CH}_2\text{CO}_2\text{Et}$), 3.50-4.00 (2H, m, C_5-H), 4.13 (4H, q, $J=7\text{Hz}$, $-\text{COCH}_2\text{CH}_3$), 4.10-4.67 (2H, m, C_2-H and $-\text{CO}-\underset{\text{CH}_3}{\text{CH}}-\text{N}$), 5.03, 5.20 (2H, AB_q, $J=12\text{Hz}$, $-\text{CH}_2-\text{Ph}$), 7.30 (5H, s, $-\text{C}_6\text{H}_5$).

The compounds shown in Table V were prepared by the same procedure as described above.

15

EXAMPLE 13

(2S)-1-[[[(2S)-Bis(ethoxycarbonylmethyl)amino]propanoyl]-2-pyrrolidinecarboxylic acid (compound 86)

- 20 (2S)-1-[[[(2S)-2-bis(ethoxycarbonylmethyl)amino]propanoyl]-2-pyrrolidinecarboxylic acid benzyl ester (compound 88) (0.50g) was dissolved in ethanol (10ml), and hydrogenated with 10% palladium on charcoal catalyst (50mg). The titled compound was obtained as a colorless oil. Yield 0.40g (quant. yild); $[\alpha]_D^{24} -52.2^\circ$ ($c=1.1$, MeOH). IR (neat, cm^{-1}): 1742, 1640, 1442, 1190, 1130, 752. NMR (CDCl_3 , δ): 1.23 (6H, t, $J=7\text{Hz}$, $-\text{CO}_2\text{CH}_2\text{CH}_3$), 1.25 (3H, d, $J=7.2\text{Hz}$, $\text{COCH}-\text{N}$), 1.67-2.50 (4H, m, C_3-H and C_4-H),

5

10

(4R)-3-[[4-(1-carboxy-3-phenylpropyl) amino]benzoyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid

15

(2S)-1-[[(2S)-2-(N-Ethoxycarbonylmethyl-N-phenylacetyl)-
amino]propanoyl]-2-pyrrolidinecarboxylic acid benzyl ester
(compound 90)

20

25

saturated sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residual oil was purified by silica gel column chromatography to give 1.3g (89%) of the titled compound: mp 110-110.5°C (benzene-hexane); $[\alpha]_D^{24} -114.0^\circ$. ($c=1.0$, MeOH). IR (KBr, cm^{-1}): 3460, 1739, 1635, 1436, 1200, 1166. NMR (CDCl_3 , δ): 1.23 (3H, d, $J=7\text{Hz}$, $-\text{CO}-\underset{\text{CH}_3}{\overset{|}{\text{CH}}}-\text{N}$)
1.28 (3H, t, $J=7\text{Hz}$, $-\text{CO}_2\text{CH}_2\text{CH}_3$), 1.67-2.50 (4H, m, $\text{C}_3\text{-H}$ and $\text{C}_4\text{-H}$), 3.60 (2H, s, $-\text{COCH}_2\text{Ph}$), 3.33-3.90 (2H, m, $\text{C}_5\text{-H}$), 4.16 (2H, q, $J=7\text{Hz}$, $-\text{COCH}_2\text{CH}_3$), 4.23 (2H, s, $-\text{N}-\text{CH}_2\text{CO}_2\text{Et}$), 4.30-4.60 (1H, m, $\text{C}_2\text{-H}$), 5.03, 5.23 (2H, ABq, $J=12.5\text{Hz}$, $-\text{CO}_2\text{CH}_2\text{Ph}$), 5.58 (1H, q, $J=7\text{Hz}$, $-\text{CO}\underset{\text{CH}_3}{\overset{|}{\text{CH}}}-\text{N}$), 7.23 (5H, s, $-\text{COCH}_2\text{C}_6\text{H}_5$), 7.30 (5H, s, $-\text{CO}_2\text{CH}_2\text{C}_6\text{H}_5$).

The compounds shown in Table V were prepared by the same procedure as described above.

EXAMPLE 15

20 .

(2S)-1-[(2S)-2-[(1-Carboxy-3-phenylpropyl)thio]propanoyl]-2-pyrrolidinecarboxylic acid (compound 79)

(2S)-1-[(2S)-2-Mercaptopropanoyl]-2-pyrrolidine-
25 carboxylic acid (2.0g), potassium carbonate (2.8g) and 2-
bromo-4-phenylbutanoic acid (2.9g) were dissolved in water
(40ml), and stirred overnight at room temperature. The

1 reaction mixture was acidified with 6N hydrochloric acid,
and extracted with ethyl acetate. The organic layer was
washed with saturated sodium chloride solution, dried
over anhydrous magnesium sulfate, and concentrated in vacuo.
5 The residual oil was purified by silica gel column chromatography to give 2.3g (62%) of the titled compound: $[\alpha]_D^{23}$
-82.2° (c=1.2, MeOH). IR (KBr, cm^{-1}): 1740, 1720, 1610, 1455,
1438, 1185, 748, 700.

10 The compounds shown in Table IV were prepared by the
same procedure as described above.

EXAMPLE 16

15 1-[[[(1-Carboxy-3-phenylpropyl)amino]acetyl]-2-(2-hydroxy-
phenyl)-5-pyrrolidinecarboxylic acid (compound 99)

1-(Chloroacetyl)-5-(2-hydroxyphenyl)-2-pyrrolidine-
carboxylic acid [mp 204-206°C(dec.), $[\alpha]_D^{24}$ +24.5° (c=1.2,
MeOH)] (2.8g) was added to a stirred solution of 2-amino-
20 4-phenylbutanoic acid (1.8g) in N sodium hydroxide (40ml).
The reaction mixture was stirred overnight at room
temperature. The solution was adjusted to pH 1.5 by 20%
hydrochloric acid, and washed with ethyl acetate. The
aqueous layer was adjusted to pH 3.0, and the separated
25 solid was collected by filtration to give 1.0g (24%) of
the titled compound. IR (nujol, cm^{-1}): 3425, 1735, 1625,
1588.

1 The compounds shown in Table V were prepared by the same
procedure as described above.

5 In EXAMPLES and TABLES I, II, III, IV and V, "a" and "b"
of compound No. represent diastereoisomers each other.
TABLES I, II, III, IV and V show various compounds and
their physical constants including the compounds specified
in EXAMPLES.

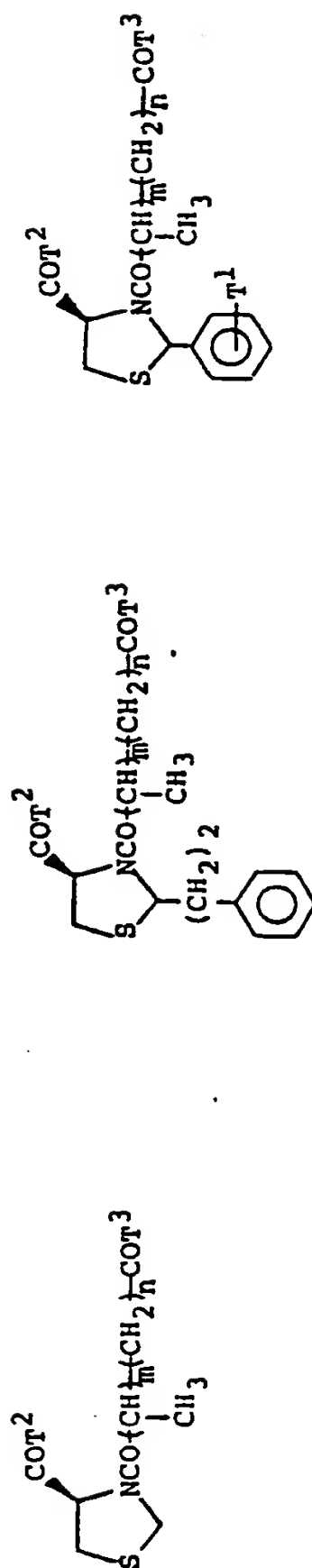
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15

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25

Table I



Compound No. 1

Compound No. 2a and 2b

Compound 3-32

Compd. No.	T ¹	T ²	T ³	m	n	Method of prep. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	[α] _D deg. (c, solv., °C)	IR spectrum		Kf #2 value (SiO ₂)
										Sampling ^{#1} method	-1 cm	
1		OH	OH	0	6	1	55	oil	-84.3 (0.8, MeOH, 26)	C	1720, 1605, 1420, 1190, 1015, 880	0.39
2a		OH	OH	0	3	5	26	oil	-19.8 (1.1, MeOH, 24)	C	1733, 1710, 1650, 1600, 1410, 1240, 1040	0.60 ^{#3}
2b		OH	OH	0	3	5	51	oil	-113.8 (1.1, MeOH, 24)	C	1730, 1650, 1610, 1410, 1240, 1042	0.55 ^{#3}
3	2-OH	OH	OH	0	1	1	65	154.0-154.5 (dec.) (H ₂ O)	+201.4 (0.7, MeOH, 25)	B	3340, 1725, 1625, 1600, 1460, 1430, 1235, 1100, 915, 770	0.25
4	2-OH	OH	OMe	1	1	6	44	oil	+161.6 (1.0, MeOH, 25)	A [#]	3380, 1723, 1624, 1235, 1200, 1174, 764	0.51
5	2-OH	OH	OH	1	1	7	75	163-164 (dec.) (EtOAc)	+174.1 (1.0, MeOH, 25)	B	3330, 1730, 1710, 1629, 1280, 1234, 856, 771	0.41

Table-continued

Compd.† No.	T ¹	T ²	T ³	m	n	Method of prep. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	[α] _D deg. (c, solv., °C)	IR spectrum		Rf ² value (SiO ₂)
										Sampling ¹ method	cm ⁻¹	
6	2-OH	OH	OH	0	2	1 5	75	190-191 (dec.) (EtOAc-MeOH)	+181.6 (1.0, MeOH, 27)	B	3210, 1720, 1618, 1602, 1245, 1173, 940, 763	0.35
7	2-OH	OH	OMe	0	2	6	83	165-166 (dec.) (EtOAc)	+164.5 (1.0, MeOH, 25)	A	3370, 1750, 1693, 1635, 1215, 1165, 755	0.47
8a	2-OH	OEt	OH	0	2	5	45	181-182 (EtOAc)	-2.8 (0.5, MeOH, 21)	A	3310, 1727, 1703, 1637, 1595, 1235, 1190, 745	0.55
8b	2-OH	OEt	OH	0	2	5	23	116-118 (EtOAc)	-311.6 (0.5, MeOH, 21)	A	3370, 1735, 1708, 1635, 1597, 1220, 1180, 760	0.55
9a	2-OH	OH	NHOH	0	2	7		172-173 (dec.) (EtOH-H ₂ O)		A	3375, 3290, 1720, 1657, 1625, 1590, 1240, 1088, 748	0.22
9b	2-OH	OH	NHOH	0	2	7		amorph.		A	3220, 1717, 1655, 1625, 1595, 1225, 1092, 752	0.33
10a	2-OH	OEt	NHOH	0	2	8		amorph.		A	3220, 1727, 1625, 1595, 1200, 1092, 753	0.25 ⁴
10b	2-OH	OEt	NHOH	0	2	8		amorph.				0.32 ⁴
11 ⁵	2-OH	OH	OMe	1	2	6		amorph.	+55.5 (0.8, MeOH, 24)	B	1738, 1630, 1585, 1310, 1258, 750	
11a	2-OH	OH	OMe	1	2	6		205-207 (dec.) (benzene)	+94.6 (0.5, MeOH, 23)	B	3110, 1730, 1625, 1610, 1192, 1121, 758	
12a	2-OH	OH	OH	1	2	7	79	168-170 (dec.) (acetone- cyclohexane)	+168.0 (0.4, MeOH, 23)	A	3370, 1718, 1625, 1598, 758	0.25 ⁴
12b	2-OH	OH	OH	1	2	7		163-164 (dec.) (acetone- cyclohexane)	+149.2 (0.4, MeOH, 23)	A	3300, 1720, 1708, 1615, 1598, 1242, 753	0.25 ⁴
13	2-OH	OH	OH	0	3	5	65	161-162 (dec.) (H ₂ O)	+153.8 (0.5, MeOH, 24)	B	3190, 1713, 1632, 1598, 1253, 1098, 943, 760	0.38
14	2-OH	OH	OEt	0	3	6	88	157-158 (dec.) (EtOAc-benzene)	+145.6 (1.0, MeOH, 25)	A	3340, 1725, 1638, 1597, 1218, 1120, 768	0.48
15	H	OH	OH	0	3	5	73	139-140 (EtOAc-MeOH)	+106.3 (1.0, MeOH, 24)	B	3170, 1753, 1709, 1631, 1423, 1177, 729	0.39

Table-continued

Compd. No.	T ¹	T ²	T ³	m	n	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	[α] _D deg. (c, solv., °C)	IR spectrum		Rf ^{#2} value (SiO ₂)
										Sampling ^{#1} method	cm ⁻¹	
16	4-CN	OH	OH	0	3	5	59	190-191 (EtOAc-MeOH)	+137.7 (1.0, MeOH, 24)	B	2225, 1710, 1665, 1412, 1258	0.31
17	2-OH	OH	OH	0	4	1	62	amorph.	+115.6 (1.0, MeOH, 24)	B	3300, 1700, 1622, 1595, 760, 723	0.43
18	2-OH	OH	OH	0	5	1	60	158-159 (dec.) (EtOAc)	+128.6 (0.5, MeOH, 25)	B	3300, 1710, 1620, 1595, 1280, 1095, 895, 850, 760	0.47
19	H	OH	OH	0	6	1	33	oil	+80.5 (1.0, MeOH, 24)			0.50
20	2-OH	OH	OH	0	6	1	61	155-157 (dec.) (EtOAc)	+134.1 (0.5, MeOH, 27)	B	3220, 1710, 1620, 1600, 1415, 1235, 1172, 950, 760	0.52
21	2-OH	OH	OH	0	7	1	63	153-154 (dec.) (EtOAc)	+70.9 (0.5, MeOH, 26)	B	3220, 1705, 1620, 1600, 1415, 1235, 1173, 1090, 830, 760	0.55
22	3-NO ₂	OH	OH	0	7	1	45	oil	+72.1 (0.4, MeOH, 27)	C	1710, 1615, 1525, 1405, 1350, 1095, 735	0.56
23	3-NO ₂	OH	OEt	0	7	6	79	oil	+72.8 (1.0, MeOH, 23)	C	1735, 1663, 1620, 1533, 1352, 1240, 1190, 728	0.57
24	2-F	OH	OH	0	7	1	53	oil	+69.9 (0.5, MeOH, 23)	C	1730, 1660, 1625, 1587, 1228, 1043, 756	0.57
25	3-F	OH	OH	0	7	1	50	oil	+63.4 (0.5, MeOH, 23)	C	1730, 1655, 1610, 1590, 1243, 1042, 775	0.57
26	4-F	OH	OH	0	7	1		oil	+57.9 (0.8, MeOH, 23)			0.51 ^{#4}
27	2-Cl 5-NO ₂	OH	OH	0	7	1	45	amorph.	+108.3 (0.5, MeOH, 23)	A	1720, 1660, 1580, 1526, 1240, 1050, 745	0.57

Table-continued

Compd. [†] No.	T ¹	T ²	T ³	m	n	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	[α] _D deg. (c, solv., °C)	IR spectrum		Rf ^{*2} value (SiO ₂)
										Sampling ^{*1} method	cm ⁻¹	
28	2-OH	OH	OH	0	8	1	58	oil	+100.3 (1.0, MeOH, 24)	C	1710, 1620, 1600, 1410, 1230, 1090, 850, 760	0.58
29	2-OH	OH	OH	0	10	1	55	123-124 (EtOAc-cyclo- hexane)	+120.4 (0.5, MeOH, 25)	B	3320, 1705, 1620, 1595, 1410, 1233, 1090, 943, 850, 760	0.61
30	3-CN	OH	OH	0	10	1	56	oil	+56.4 (0.3, MeOH, 23)			^{*4} 0.56
31	2-OH	OH	OH	0	12	1	59	amorph.	+101.4 (1.0, MeOH, 24)	B	3280, 1700, 1620, 1575, 760, 722	0.52
32	3-CN	OH	OH	0	12	1	43	oil	+61.7 (0.6, MeOH, 23)			^{*4} 0.53

[†] a and b represent diastereoisomers of the compound.

^{*1} A; KBr disk, B; nujol mull, C; neat.

^{*2} EtOAc-CHCl₃-AcOH (10:5:3).

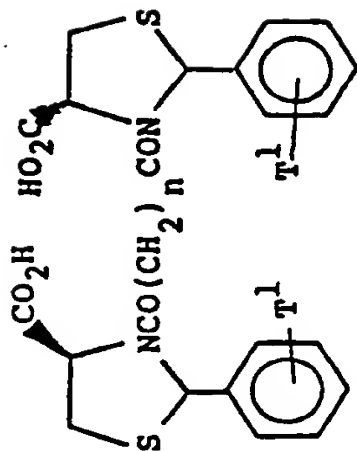
^{*3} CHCl₃-EtOH-AcOH (10:2:1).

^{*4} EtOAc-CHCl₃-AcOH (7:5:1).

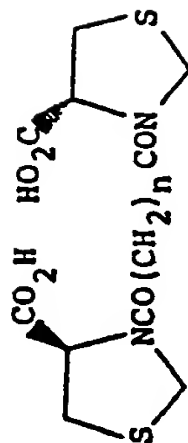
^{*5} Dicyclohexylamine salt.

38

Table II



Compound No. 33-37, 39-62



Compound No. 38

Compd. No.	T ¹	n	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	[α] _D deg. (c, solv., °C)	IR spectrum		Rf value (SiO ₂)
							Sampling method	cm ⁻¹	
33	2-OH	4	2	73	124-128 (MeOH)	+182.2 (1.0, DMF, 24)	B	3280, 1726, 1620, 1596, 775,	0.23
34	2-OH	5	2	67	oil	+106.1 (0.5, MeOH, 26)	C	1725, 1625, 1600, 1410, 1235, 1095, 1045, 850, 765	0.27
35	3-NO ₂ ^{*5}	5	4	69	111-113 (dec.) (H ₂ O)	+88.2 (0.5, MeOH, 25)	B	1635, 1585, 1520, 1355 1095, 730	0.28
36	3-CN	5	3	59	105-112 (H ₂ O)	+115.0 (1.0, MeOH, 25)	B	2270, 1735, 1640, 1610, 1195, 790	0.33
37	4-CN	5	3	52	amorph.	+148.2 (0.9, MeOH, 25)	B	2255, 1731, 1655, 1620, 785	0.32
38		6	2	77	oil	-124.5 (0.5, MeOH, 26)	C	1720, 1580, 1410, 1180, 1015, 880	0.09
39	H	6	2	79	amorph.	+97.4 (1.0, MeOH, 24)	B	1720, 1625, 1585, 732	0.42

Table-continued

Compd. No.	T ¹	n	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	[α] _D deg. (c, solv., °C)	IR spectrum		Rf ^{#2} value (SiO ₂)
							Sampling ^{#1} method	cm ⁻¹	
40	2-OH	6	2	86	amorph.	+123.6 (0.5, MeOH, 27)	B	1720, 1620, 1600, 1230, 1090, 855, 765	0.34
41	3-NO ₂	6	2	56	amorph.	+97.5 (0.5, MeOH, 21)	B	1730, 1650, 1605, 1520, 1345, 1095, 730	0.34
42	3-CN	6	2	58	amorph.	+98.3 (0.9, MeOH, 25)	B	2250, 1730, 1640, 1615, 1200, 790	0.38
43	4-CN	6	2	41	amorph.	+130.2 (0.9, MeOH, 25)	B	2248, 1729, 1650, 1618, 790	0.36
44	2-OH	7	2	75	amorph.	+142.7 (0.5, MeOH, 26)	B	1720, 1620, 1600, 1410, 1230, 1173, 1090, 855, 763	0.40
45	2-NO ₂	7	2	47	amorph.	+191.2 (0.6, MeOH, 25)	B	1735, 1655, 1515, 1345, 1190, 730	0.38
^{#6} 46	3-NO ₂	7	9	96	61-63 (benzene)	+79.4 (1.0, MeOH, 23)	A	1740, 1660, 1530, 1350, 1198, 725	0.57
47	3-NO ₂	7	2	82	amorph.	+96.2 (0.5, MeOH, 27)	B	1725, 1615, 1520, 1445, 1350, 1095, 730	0.41
48	4-NO ₂	7	2	53	amorph.	+118.5 (0.5, MeOH, 25)	B	1730, 1650, 1600, 1510, 1345, 1185, 1110, 735	0.48
49	3-CN	7	3	65	amorph.	+112.1 (1.1, MeOH, 25)	B	2250, 1729, 1640, 1610, 790	0.41
^{#5} 50	2-F	7	4	85	140-220 (dec.) (H ₂ O)	+117.5 (1.0, MeOH, 24)	A	1580, 1225, 1173, 758	0.50
^{#5} 51	3-F	7	4	88	195-210 (dec.) (H ₂ O)	+103.9 (0.5, MeOH, 25)	A	1590, 1238, 1142, 767	0.50
52	4-F	7	2	76	oil	+75.8 (1.0, MeOH, 23)			^{#3} 0.39

Table-continued

Compd. No.	T ¹	Method		mp (°C) (Recrystn. solvent)	[α] _D deg. (c, solv., °C)	IR spectrum cm ⁻¹	Rf ^{*2} value (SiO ₂)
		n	of prepn. (Examp. No.)			Sampling ^{*1} method	
53	2-Cl 5-NO ₂	7	2	79 amorph.	+167.9 (0.5, MeOH, 23)	A 1725, 1640, 1575, 1520, 1342, 1047, 740	0.51
54	2-OH 5-SO ₂ NH ₂	7	2	75 amorph.	+140.9 (0.6, MeOH, 23)	B 1725, 1620, 1595, 1310, 1150, 930	0.42 ^{*4}
55	2-OH	8	2	68 amorph.	+122.1 (1.0, MeOH, 24)	B 3300, 1730, 1628, 1575, 767, 725	0.45
56	3-CN	8	2	47 amorph.	+104.6 (1.0, MeOH, 25)	B 2245, 1726, 1630, 1610, 790	0.37
57	3-NO ₂	8	2	84 amorph.	+102.2 (0.5, MeOH, 25)	A 1735, 1620, 1523, 1190, 728	0.47
58 ^{*5}	3-NO ₂	8	4	74 amorph.	+93.9 (0.5, MeOH, 23)	A 1597, 1520, 1269, 1096, 723	
59	2-OH	10	2	61 99-100.5 (dec.) (EtOAc-benzene)	+124.7 (0.5, MeOH, 27)	B 3300, 1740, 1620, 1600, 1565, 1230, 1160, 1090, 895, 770	0.49
60 ^{*5}	3-CN	10	4	63 190-195 (H ₂ O)	+109.3 (0.5, H ₂ O, 23)	B 3400, 2240, 1640, 1600, 1208, 778, 720	
61	2-OH	12	2	66 amorph.	+69.5 (1.0, MeOH, 24)	B 3300, 1728, 1630, 1590, 762, 725	0.45
62 ^{*5}	3-CN	12	4	52 amorph.	+104.2 (0.5, MeOH, 23)	B 3400, 2225, 1605, 1320, 1207, 775, 720	0.46 ^{*3}

^{*1} A; KBr disk, B; nujol mull, C; neat.^{*2} EtOAc-CHCl₃-AcOH (10:5:3).^{*3} EtOAc-CHCl₃-AcOH (7:5:1).^{*4} CHCl₃-MeOH-AcOH (3:1:1).^{*5} Disodium salt.^{*6} Dimethyl ester.

Table III



Compound No. 63-68

Compound No. 69-71

Compd. No.	T ¹	W	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	[α] _D deg. (c, solv., °C)	IR spectrum		Rf ^{#2} value (SiO ₂)
							Sampling ^{#1} method	cm ⁻¹	
63	2-OH	-CH ₂ COCH(COCH ₃)-	5	31	amorph.	+149.2 (1.2, MeOH, 25)	B	1743, 1720, 1630, 1600, 1238	0.38 ^{#3}
64	2-OH	-CH ₂ -O-CH ₂ -	1	35	amorph.	+138.6 (1.1, MeOH, 25)	A	3300, 1726, 1640, 1453, 1234, 1142	0.24 ^{#4}
65	3-NO ₂	-(CH ₂) ₂ -C ₆ H ₄ -(CH ₂) ₂ -	1	36	amorph.	+81.7 (0.9, MeOH, 24)	A	3400, 1702, 1618, 1525, 1400, 1347	0.55 ^{#3}
66	2-OH	-(CH ₂) ₂ -O-(CH ₂) ₂ -	1	33	136-137 (EtOAc)	+147.6 (0.5, MeOH, 25)	B	3320, 1750, 1710, 1625, 1595, 1235, 1110, 855, 770	0.28
67	2-OH	-(CH ₂) ₂ -S-(CH ₂) ₂ -	1	40	159-160 (dec.) (EtOAc)	+136.4 (0.5, MeOH, 27)	B	3360, 1710, 1627, 1599, 1435, 1235, 1099, 852, 763	0.42
68	2-OH	-(CH ₂) ₂ -S-(CH ₂) ₂ -S-(CH ₂) ₂ -	1	35	amorph.	+78.1 (1.0, MeOH, 24)	B	3300, 1715, 1627, 1590, 760	0.31
69	3-NO ₂	-(CH ₂) ₂ -C ₆ H ₄ -(CH ₂) ₂ -	2	44	amorph.	+106.9 (1.1, MeOH, 24)	A	3425, 1730, 1640, 1525, 1400, 1350	0.38 ^{#3}

Table-continued

Compd. No.	T ¹	W	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	[α] _D deg. (c, solv., °C)	IR spectrum		Rf ^{#2} value (SiO ₂)
							*Sampling ^{#1} method	cm ⁻¹	
70	2-OH	$\{CH_2\}_2O-\{CH_2\}_2$	2	47	amorph.	+83.0 (0.5, MeOH, 26)	B	1720, 1625, 1600, 1230, 1090, 850, 760	0.15
71	2-OH	$\{CH_2\}_2S-\{CH_2\}_2$	2	53	amorph.	+129.3 (0.5, MeOH, 27)	B	1720, 1620, 1600, 1420, 1230, 1093, 852, 763	0.30

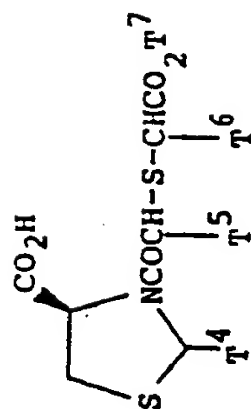
*1 A; KBr disk, B; nujol mull.

*2 EtOAc-CHCl₃-AcOH (10:5:3).

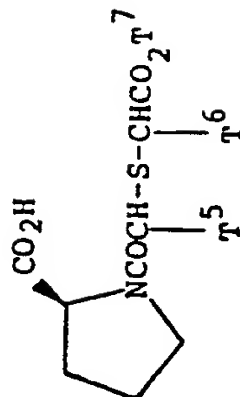
*3 EtOAc-EtOH-AcOH (40:1:1).

*4 CHCl₃-EtOH-AcOH (10:2:1).

Table IV



Compound No. 72-76



Compound No. 77-80

Compd. No.	T ⁴	T ⁵	T ⁶	T ⁷	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	[α] _D deg. (c, solv., °C)	IR spectrum		Rf value (SiO ₂)
									Sampling ^{*1} method	cm ⁻¹	
72a	H	CH ₃	Ph	H	10	38	151-153 (EtOAc)	+8.6 (1.0, MeOH, 23)	A	3030, 1737, 1720, 1615, 1413, 1215, 1150, 717	0.26 ^{*3}
72b	H	CH ₃	Ph	H	10	49	oil	-161.5 (1.0, MeOH, 23)	C	1735, 1623, 1413, 1243, 1170, 1043, 699	0.22 ^{*3}
73		H	CH ₂ CH ₂ Ph	H	10	81	amorph.	+122.1 (1.2, MeOH, 25)	A	1720-1710, 1625, 1600, 1400, 1235, 752, 698	0.74
74	H	CH ₃	CH ₂ CH ₂ Ph	H	10	52	amorph.	-97.9 (1.1, MeOH, 25)	A	1720, 1620, 1415, 750, 700	0.65
75a	H	CH ₂ Ph	H	H	10	37	oil	-52.2 (1.2, MeOH, 25)	C	1720, 1620, 1422, 1217, 756	0.13 ^{*4}
75b	H	CH ₂ Ph	H	H	10	46	oil	-60.4 (1.0, MeOH, 25)	C	1722, 1620, 1420, 1215, 755	0.13 ^{*4}
76	H	CH ₂ CH ₂ Ph	H	H	10	84	oil	-61.2 (1.3, MeOH, 24)	C	1735, 1630, 1615, 1420, 1242, 1172, 1043, 702	0.66

Table-continued

Compd. No.	T ⁴	T ⁵	T ⁶	T ⁷	Method of prepn. (Examp. No.)	Yield (%)	mp (C°) (Recrystn. solvent)	[α] _D deg. (c, solv., °C)	IR spectrum		Rf ^{*2} value (SiO ₂)
									Sampling ^{*1} method	cm ⁻¹	
77		H	COPh	Et	15	36	oil	-46.2 (0.8, MeOH, 30)	C	1733, 1678, 1632, 1610, 1447, 1258, 1187, 1025, 1001, 751	0.32 ^{*3}
78		H	CH ₂ CH ₂ Ph	H	15	46	oil	-48.4 (1.1, MeOH, 26)	C	1730, 1610, 1450, 1240, 1190, 750, 703	0.72 ^{*5}
79		CH ₃	CH ₂ CH ₂ Ph	H	15	62	amorph.	-82.2 (1.2, MeOH, 23)	A	1740, 1720, 1610, 1455, 1438, 1185, 748, 700	0.38
80		H	COCH ₃	Et	15	45	oil	-49.6 (0.9, MeOH, 30)	C	1736, 1597, 1398, 1378, 1333, 1250, 1191, 1047, 860, 752	0.29 ^{*3}

[†] a and b represent diastereoisomers of the compound.

^{*1} A; KBr disk, C; neat.

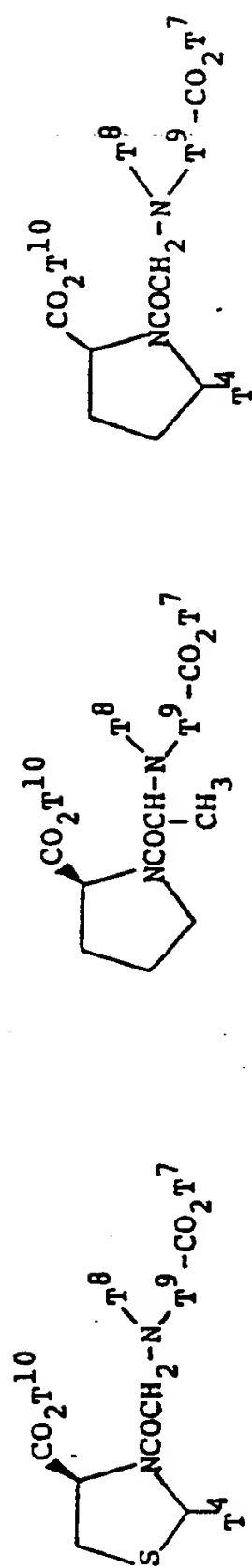
^{*2} EtOAc-CHCl₃-AcOH (10:5:3).

^{*3} Benzene-EtOAc-EtOH-AcOH (14:14:2:1).

^{*4} Benzene-EtOAc-AcOH (25:25:1).

^{*5} CHCl₃-EtOH-AcOH (10:2:1)



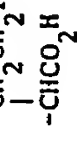
Table V



Compound No. 81-85 Compound No. 86-98, 100-102 Compound No. 99

Compd. No.	T ⁴	T ⁷	T ⁸	T ⁹	T ¹⁰	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	(α) _D deg. (c, solv., °C)	IR spectrum		RF value (SiO ₂)
										Sampling method	cm ⁻¹	
81		H	H	-CH ₂ -	H	11	48.2	181-182 (dec.) (H ₂ O)	+271.2 (0.5, N NaOH, 24)	A	3400, 3200, 1740, 1672, 1560, 1440, 1380, 1335, 1210, 752	0.25 ²
82		H	H	-CH ₂ -	H	11	32.8	150-155 (H ₂ O)	+94.7 (0.5, N NaOH, 23)	B	3420, 3210, 1650, 1240, 839, 790	0.45 ³
83		H	H		H	11	44.8	150-153 (dec.) (EtOH-ether)	+86.5 (0.4, MeOH, 26)	A	3370-2900, 1655, 1602, 1175	0.74 ⁴
84		H	H		H	11	50.3	172-173 (dec.) (EtOAc)	+78.9 (0.8, MeOH, 25)	A	3350, 1720, 1670, 1644, 1236, 744	0.69 ⁴
85		H	H		H	11	27.2	174-175 (dec.) (H ₂ O)		A	3400, 1720, 1660, 1610, 1492, 1452, 1240, 752, 700	0.21 ⁵
86	H	Et	CH ₂ CO ₂ Et	-CH ₂ -	H	13	quant.	oil	-52.2 (1.1, MeOH, 24)	C	1742, 1640, 1442, 1190, 1130, 752	0.21 ⁵

Table-continued

Compd. [†] No.	T ⁴	H	T ⁷	T ⁸	T ⁹	T ¹⁰	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	[α] _D deg. (c, solv., °C)	IR spectrum		Rf value (SiO ₂)
											Sampling method	cm ⁻¹	
87	H	H	H	CH ₂ CO ₂ H	-CH ₂ -	H	7	26	amorph.	-32.8 (1.0, MeOH, 24)	B	3400, 1720, 1640, 1460, 1380	0.10 ^{*2}
88	H	H	Et	CH ₂ CO ₂ Et	-CH ₂ -	CH ₂ Ph	12	45.2	oil	-67.9 (1.2, MeOH, 24)	C	3460, 1742, 1642, 1428, 1180	0.70 ^{*5}
89a	H	H	H	H		H	16	33	216-218 (dec.) (H ₂ O)	-141.1 (0.3, MeOH, 23)	B	2600, 1743, 1550, 1250, 1230, 800	0.20 ^{*6}
89b	H	H	H	H		H	16	45	218-226 (dec.) (H ₂ O)	+1.5 (0.5, MeOH, 23)	B	3310, 1610, 1575, 1160, 742	0.20 ^{*6}
90	H	H	Et	COCH ₂ Ph	-CH ₂ -	CH ₂ Ph	14	89	110-110.5 (benzene- <i>n</i> -hexane)	-114.0 (1.0, MeOH, 24)	A	3460, 1739, 1635, 1436, 1200, 1166	0.45 ^{*7}
91	H	H	Et	COCH ₂ Ph	-CH ₂ -	H	13	quant.	oil	-99.7 (1.1, MeOH, 23)	D	1743, 1640, 1445, 1187	0.35 ^{*5}
92	H	H	H	COCH ₂ Ph	-CH ₂ -	H	7	83	205-206 (EtOAc-MeOH)	-123.5 (1.0, MeOH, 24)	A	3430, 1727, 1635, 1598, 1426, 1184	0.38 ^{*8}
93	H	H	Et	CO(CH ₂) ₂ Ph	-CH ₂ -	CH ₂ Ph	14	93	oil	-93.2 (1.0, MeOH, 24)	C	1746, 1655, 1647, 1447, 1188	0.51 ^{*7}
94	H	H	Et	CO(CH ₂) ₂ Ph	-CH ₂ -	H	13	quant.	oil	-94.7 (1.2, MeOH, 23)	D	1746, 1642, 1449, 1190,	0.38 ^{*5}
95	H	H	H	CO(CH ₂) ₂ Ph	-CH ₂ -	H	7	96	amorph.	-104.3 (1.0, MeOH, 24)	A	3440, 1735, 1610, 1450, 1185	0.45 ^{*8}
96	H	H	Et	CH ₂ Ph	-CH ₂ -	CH ₂ Ph	12	46	oil	-66.0 (1.2, MeOH, 25)	D	1740, 1639, 1450, 1425, 1185	0.57 ^{*7}
97	H	H	H	CH ₂ Ph	-CH ₂ -	H	7	87	amorph.	-59.0 (1.1, MeOH, 25)	A	3420, 1720, 1638, 1448, 1385	0.17 ^{*2}
98	H	H	H	COCH ₃		H	14	62	195-196 (dec.) (EtOAc)		B	1758, 1720, 1615, 1600, 1380, 750, 700	

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Table-continued

Compd. No.	T ⁴	T ⁷	T ⁸	T ⁹	T ¹⁰	Method of prepn. (Examp. No.)	Yield (%)	mp (°C) (Recrystn. solvent)	[α] _D deg. (c, solv., °C)	IR spectrum		Rf value (SiO ₂)
										Sampling ^{*1} method	cm ⁻¹	
99 ^{*11}		H	CH ₂ CH ₂ Ph	H	H	16	24	amorph.		B	3425, 1735, 1625, 1588	0.66 ^{*2}
100	H	Et		CH ₂ Ph	14	37	oil		-46.9 (0.5, MeOH, 23)	C	1740, 1642, 1453, 1425, 1170, 740	0.20 ^{*9}
101	H	Et		H	13	90	oil		-35.9 (0.5, MeOH, 23)			0.25 ^{*2}
102	H	H		H	7	90	228-230 (dec.) (MeOH)		-33.9 (0.4, MeOH, 23)	B	3450, 1720, 1610, 1305, 1228, 1200, 680	0.34 ^{*10}

[†] a and b represent diastereoisomers of the compound.

^{*1} A; KBr disk, B; nujol mull, C; Neat, D; liquid cell (CHCl₃).

^{*2} n-BuOH-AcOH-H₂O (4:2:1).

^{*3} n-BuOH-AcOH-H₂O (4:1:2).

^{*4} EtOAc-CHCl₃-AcOH (10:5:3).

^{*5} EtOAc-EtOH-AcOH (40:1:1).

^{*6} EtOAc-CHCl₃-AcOH (7:5:1).

^{*7} Benzene-EtOAc-AcOH (25:25:1).

^{*8} CHCl₃-EtOH-AcOH (10:2:1).

^{*9} EtOAc

^{*10} n-Propanol-28% aq. NH₃ (7:3).

^{*11} Starting material: 1-(chloroacetyl)-5-(2-hydroxyphenyl)-2-pyrrolidineneacetic acid; mp 204-206°C (dec.), [α]_D²⁴ +24.5° (c=1.2, MeOH), IR (nujol, cm⁻¹) 3370, 1698, 1645, 1610, 1595, 1238, 758.

1 PHARMACOLOGICAL TEST 1

It has been known that aldose reductase participates in diabetic cataract which is one of the diabetic complications and that appearance is retarded or depressed by inhibition of the aldose reductase [Acta Societatis Ophthalmologicae Japonicae, 80, 1362 (1976)].
5 The following method is used for the present test.

(Method)

10 Aldose reductase is purified from rat lenses according to the method of Hoyman et al. [J. Biol. Chem., 240, 877 (1965)]. Action of the compounds (I) of this invention is evaluated by measurement of optical density according to the J.H. Kinoshita's method [Invest. Oph-
15 thal., 13, 713 (1974)]. The reaction mixture for the measurement of the aldose reductase activity is 3.0ml [0.007M phosphate buffer solution (pH 6.2), 0.46M lithium sulfate, 5×10^{-5} M NADPH, 4×10^{-4} M DL glyceraldehyde, 10U aldose reductase, 10^{-4} to 10^{-10} M the compounds (I)]
20 as total volume, and the absorbance thereof is measured at 340nm.

(Result)

Table VI shows that the compounds (I) of this in-
25 vention have a strong aldose reductase inhibition effect.

1 Table VI. Inhibitory Activity of the Thiazolidine
Compounds against Aldose Reductase

5	Compd. No.	IC ₅₀ (M) *1
	22	8.2 x 10 ⁻¹⁰
	23	1.1 x 10 ⁻⁸
	47	1.6 x 10 ⁻¹⁰
	56	1.7 x 10 ⁻⁹
10	57	5.4 x 10 ⁻⁹
	Control *2	1.0 x 10 ⁻⁷

*1 Molar concentration of a compound producing
50% inhibition of aldose reductase.

15 *2 Quercitrin: referred to Acta Societatis
Ophthalmologicae Japonicae, 80, 1369-1370 (1976).

PHARMACOLOGICAL TEST 2

20 As the method of measurement of angiotensin I-
converting enzyme activity, bioassay for the contractile
response of isolated smooth muscle or the pressor re-
sponse of normal animals and biochemical assay for the
enzyme isolated from lung or other organs of animals
are known. The former is found more advantageous than
25 the latter for the examination of the conversion of
angiotensin I to angiotensin II in vivo.

1 In the present study, therefore, we adopted the
bioassay for contractile response of isolated guinea
pig ileum to angiotensin I.

5 (Method)

Isolated guinea pig ileum was suspended in the or-
gan bath containing 20ml of Tyrode's solution of 30°C
gassed with 95% O₂ + 5% CO₂. The contraction induced
by the addition of angiotensin I (0.1µg/ml) at intervals
10 of 10 minutes was recorded on a recticorder (Nihon Kodan)
for 90 seconds using FD pick up (ST-1T-H, Nihon Kodan)

The test compounds were added to the bath 5 minutes
before the addition of angiotensin I.

The inhibitory activity of angiotensin I-convert-
15 ing enzyme was calculated by the following formula.

$$\frac{A - B}{A} \times 100$$

A: contractile intensity of angiotensin I
before addition of the compound

20 B: contractile intensity of angiotensin I
after addition of the compound

From the fact that kininase II, which destroys
bradykinin having contractive action on isolated guinea
pig ileum, is thought to be identical with angiotensin
I-converting enzyme augmentation of the contractile
25 response to bradykinin by test compounds was examined

1 by using bradykinin (0.005 μ g/ml) in place of angiotensin
I according to the above mentioned method.

(Result)

5 Concentration of a number of the compounds of this
invention, which produced 50% inhibition of angiotensin
I activity or augmentation of bradykinin activity in-
ducing the contraction of guinea pig ileum, fell in the
range of 10^{-7} ~ 10^{-9} M.

10 PHARMACOLOGICAL TEST 3

The activity of angiotensin I-converting enzyme
was measured by spectrophotometry according to the method
of D.W. Cushman and H.S. Cheung [Biochem. Pharmacol.,
20, 1637 (1971)]. That is, the absorbance of hippuric
15 acid was measured, which is liberated by incubating
hippuryl-L-histidyl-L-leucine (HHL) as substrate in the
presence of angiotensin I-converting enzyme extracted
from rabbit lung.

20 (Method)

The reaction mixture is as follows:

100mM phosphate buffer (pH 8.3)

300mM sodium chloride

5mM HHL

25 10^{-3} ~ 10^{-9} M enzyme inhibitor

5mU enzyme

1 0.25ml of the above mixture was incubated at 37°C
for 30 minutes and the reaction was stopped by adding
0.25ml of 1 N hydrochloric acid. To this solution,
1.5ml of ethyl acetate was added in order to extract
5 hippuric acid. 1.0ml of ethyl acetate layer was col-
lected and evaporated to dryness, and the residue ob-
tained was dissolved in 1.0ml of water. The absorbance
of this solution was measured at 228nm.

The inhibitory activity of angiotensin I-converting
10 enzyme was calculated by the following formula:

$$\text{Percent inhibition} = \frac{A - B}{A} \times 100$$

A: absorbance of reaction solution before
addition of the compound

B: absorbance of reaction solution after
15 addition of the compound

Concentration of compound producing 50% inhibition of
angiotensin I-converting enzyme (IC₅₀)

The solution containing compounds at the concentra-
20 tion of $1 \times 10^{-3}M$ to $1 \times 10^{-9}M$ was incubated and percent
inhibition at each concentration was calculated accord-
ing to the above formula, and then IC₅₀, concentration
of the compound producing 50% inhibition of the enzyme
activity, was determined.

25 (Result)

IC₅₀ of a number of the compounds of this invention,

1 fell in the range of $10^{-7} \sim 10^{-10}$ M.

TOXICITY TEST

5 The acute toxicity of compounds 47 and 56 is 1000 - 1500mg/kg.

(Experimental animals)

The male ddy-std. strain mice (4 weeks of age, weighing 19-21g) were placed in a breeding room of constant temperature and humidity ($23 \pm 1^\circ\text{C}$, $55 \pm 5\%$) and fed freely pellet diet (CE-2, Clea Japan, Inc.) and water ad. libitum for a week. The mice showing the normal growth were selected for the experiment.

15 (Method of administration)

Test compounds are dissolved in distilled water and administered (i.v.) in a dose of 0.5ml/20g body weight.

It is found in the above pharmacological and toxicity test that the compounds (I) of this invention are useful as drugs for therapy or prophylaxis of the diabetic complications and as antihypertensive agents.

In case the compounds are used for preventing or relieving diabetic complications, the dosage forms are tablet, capsule, granule, powder, suppository, injection, ophthalmic solution, ophthalmic ointment, etc. These preparations can also contain general excipients.

1 On the other hand, in case the compounds are used
 for reducing blood pressure, they can be given with the
 combination of diuretics such as probenecid, carinamide,
 hydroflumethiazide, furosemide, and bumetanide same as
 5 other antihypertensive agents. The compounds can be
 administered either orally or parenterally. The dosage
 forms are tablet, capsule, granule, powder, suppository,
 injection, etc. In the treatment of hypertension, these
 preparations can contain not only general excipients
 10 but also other antihypertensive agents such as reserpine,
 α -methyldopa, guanethidine, clonidine, hydralazine, etc.,
 or β -adrenergic blocking agents such as propranolol,
 alprenolol, pindolol, bufetolol, bupranolol, bunitrolol,
 practolol, oxprenolol, indenolol, timolol, bunolol, etc.
 15 The dose is adjusted depending on symptom, dosage
 form, etc. But, usual daily dosage is 1 to 5000mg, pref-
 erably 10 to 1000mg, in one or a few divided doses.

EXAMPLES OF FORMULATION

20 (1) Oral drug

(a) tablet

	compound 13	50mg
	lactose	120mg
	crystalline cellulose	60mg
25	calcium carboxymethylcellulose	7mg
	magnesium stearate	3mg
	<hr/>	
	Total	240mg

1	compound 22	100mg
	lactose	95mg
	crystalline cellulose	45mg
	calcium carboxymethylcellulose	7mg
5	magnesium stearate	3mg
	Total	240mg
	compound 23	150mg
	lactose	60mg
10	crystalline cellulose	30mg
	calcium carboxymethylcellulose	7mg
	magnesium stearate	3mg
	Total	250mg
15	compound 56	150mg
	lactose	60mg
	crystalline cellulose	30mg
	calcium carboxymethylcellulose	7mg
20	magnesium stearate	3mg
	Total	250mg
	compound 74	150mg
	lactose	60mg
25	crystalline cellulose	30mg
	calcium carboxymethylcellulose	7mg

1	magnesium stearate	3mg,
	<hr/>	
	Total	250mg
	compound 88	150mg
5	lactose	60mg
	crystalline cellulose	30mg
	calcium carboxymethylcellulose	7mg
	magnesium stearate	3mg
	<hr/>	
10	Total	250mg

The tablets may be treated with common film-coating and further with sugar-coating.

	(b) granule	
15	compound 13	30mg
	polyvinylpyrrolidone	25mg
	lactose	385mg
	hydroxypropylcellulose	50mg
	talc	10mg
20	<hr/>	
	Total	500mg
	compound 22	30mg
	polyvinylpyrrolidone	25mg
25	lactose	385mg
	hydroxypropylcellulose	50mg

1	talc	10mg
	Total	500mg
5	compound 94	30mg
	polyvinylpyrrolidone	25mg
	lactose	385mg
	hydroxypropylcellulose	50mg
	talc	10mg
10	Total	500mg
	(c) powder	
	compound 13	250mg
	lactose	240mg
15	starch	480mg
	colloidal silica	30mg
	Total	1000mg
20	compound 65	300mg
	lactose	230mg
	starch	440mg
	colloidal silica	30mg
	Total	1000mg
25	compound 79	300mg
	lactose	230mg

1	starch	440mg
	colloidal silica	30mg
	Total	1000mg
5	compound 100	300mg
	lactose	230mg
	starch	440mg
	colloidal silica	30mg
10	Total	1000mg
	(d) capsule	
	compound 13	50mg
	lactose	102mg
15	crystalline cellulose	36mg
	colloidal silica	2mg
	Total	190mg
	compound 23	100mg
20	lactose	52mg
	crystalline cellulose	36mg
	colloidal silica	2mg
	Total	190mg
25	compound 74	200mg
	glycerin	179.98mg

1	butyl p-hydroxybenzoate	0.02mg
	<hr/>	
	Total	380mg

5	compound 81	30mg
	glycerin	349.98mg
	butyl p-hydroxybenzoate	0.02mg
	<hr/>	
	Total	380mg

10	compound 98	200mg
	glycerin	179.98mg
	butyl p-hydroxybenzoate	0.02mg
	<hr/>	
	Total	380mg

15 (2) Injection

(a) 1 to 30mg of compound 9B is contained in 1ml of the aqueous solution (pH 6.5-7.0).

20 (b) 1 to 30mg of compound 73 is contained in 1ml of the aqueous solution (pH 6.5-7.0).

(3) Ophthalmic solution

The following composition is contained in 5ml of the aqueous solution (pH 6.0).

25

Compound 23	50mg
-------------	------

1 propyl p-hydroxybenzoate 0.7mg
 methyl p-hydroxybenzoate 1.3mg
 sodium hydroxide proper quantity

5 (4) Ophthalmic ointment

 The following composition is contained in 1g.

 compound 22 20mg
 white petrolatum 889.8mg
10 mineral oil 100mg
 butyl p-hydroxybenzoate 0.2mg

(5) Suppository

 The following composition is contained in 1g.

15 compound 47 50mg
 polyethyleneglycol 1000 800mg
 polyethyleneglycol 4000 150mg

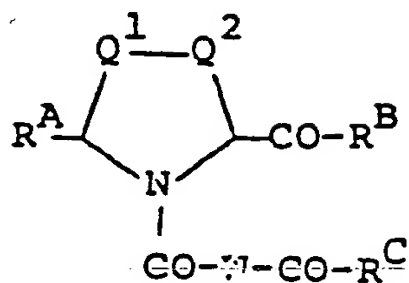
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1 CLAIMS

1. A compound of the formula [I]

5



[I]

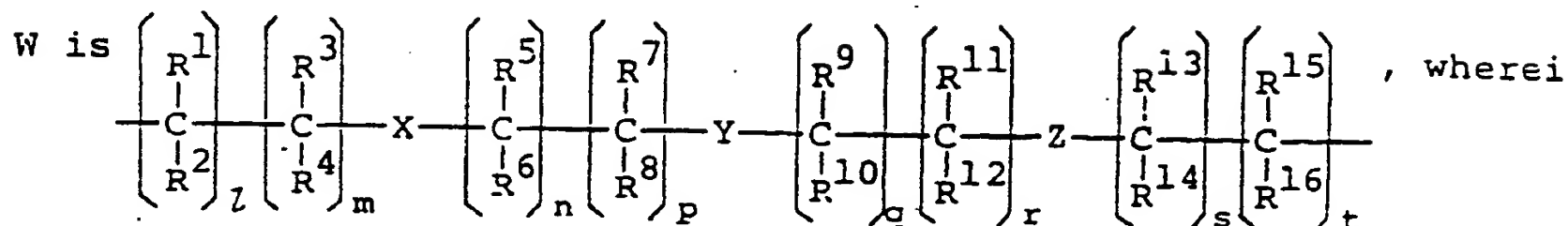
wherein

10 Q^1 and Q^2 each is methylene or sulfur, but Q^1 and Q^2 are not sulfur at the same time;

R^A is R^a or R^b ;

R^B and R^C each is R^c ;

15



X, Y and Z each is single bond, $-CH_2-$, $\begin{array}{c} -C=C- \\ | \quad | \\ R^{17} \quad R^{18} \end{array}$, $-C \equiv C-$, $\begin{array}{c} \text{---} \bigcirc \text{---} \\ | \\ R^{19} \end{array}$,
 -O-, -CO-, -S-, -SO-, -SO₂-, $\begin{array}{c} -C- \\ || \\ N-R^{20} \end{array}$, -NHCONH-, $\begin{array}{c} \text{---} \bigcirc \text{---} \\ | \quad | \\ N \quad N \end{array}$ or $\begin{array}{c} -N- \\ | \\ R^{21} \end{array}$;

20

l, m, n, p, q, r, s and t each is 0, 1, 2 or 3;
 $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}$ and R^{21} each is R^d ;

R^A is R^b when W is $\begin{array}{c} -CH-NH-C- \\ | \quad | \quad | \\ R^{22} \quad R^{23} \quad R^{24} \end{array}$ or $\begin{array}{c} -CH-(CH)_0-2 \\ | \quad | \\ R^{25} \quad R^{26} \end{array}$, wherein $R^{22}, R^{23}, R^{24}, R^{25}$ and R^{26} each is R^d ;

25

R^a is selected from the group consisting of
 (i) hydrogen, lower alkyl and lower alkenyl, and
 (ii) lower alkyl and lower alkenyl substituted by at least one
 substituent selected from the group consisting of lower alkyl,

1 lower alkenyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkyl amino, acylamino, mercapto, acylmercapto, lower alkylthio, carbonyl, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

5

R^b is selected from the group consisting of

(a) (i) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl, and
 (ii) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl, and
 (iii) carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl and heteroaryloxycarbonyl;

15

(b) (i) phenyl and naphthyl, and

(ii) phenyl and naphthyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, aralkyloxy, aryloxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

20

(c) (i) furyl, thienyl and pyridyl, and

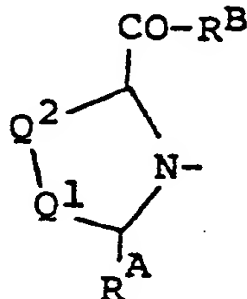
(ii) furyl, thienyl and pyridyl substituted by at least one substituent selected from the group consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy, aralkyloxy, aryloxy, acyloxy, halogen, nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

25

1 R^C is selected from the group consisting of
 (a) (i) hydroxy, lower alkoxy and amino, and
 (ii) lower alkoxy and amino substituted by at least one substituent
 selected from the group consisting of lower alkyl, aralkyl,
 heteroaralkyl, aralkenyl, heteroaralkenyl, hydroxy, lower alkoxy,
 5 aralkyloxy, heteroaralkyloxy, aryloxy, heteroaryloxy, acyloxy,
 aryl, heteroaryl, substituted aralkyl and substituted aryl
 wherein the substituent is lower alkyl, lower alkoxy, halogen
 or amino;

(b) (i) aryloxy and heteroaryloxy, and
 (ii) aryloxy and heteroaryloxy substituted by at least one
 10 substituent selected from the group consisting of lower alkyl,
 hydroxy, lower alkoxy, halogen and amino, and

(c)



15 R^d is selected from the group consisting of
 (a) (i) hydrogen, lower alkyl, lower alkenyl, aralkyl, hetero-
 aralkyl, alkanoyl, arylalkanoyl, heteroarylalkanoyl, hydroxy,
 carboxy, amino, mercapto and sulfo, and
 (ii) lower alkyl, lower alkenyl, aralkyl, heteroaralkyl, alkanoyl,
 arylalkanoyl, heteroarylalkanoyl, hydroxy, carboxy, amino,
 mercapto and sulfo substituted by at least one substituent
 20 selected from the group consisting of lower alkyl, lower alkenyl,
 lower alkoxy, lower alkanoyl, aryl, heteroaryl, acyloxy,
 aroyl, hydroxy, carboxy, amino, guanidino, mercapto, acylamino,
 acylmercapto, lower alkoxycarbonyl, sulfo, halogen, nitro,
 cyano, sulfamoyl, lower alkylaminosulfonyl, lower alkylthio
 and lower alkylsulfinyl;

25 (b) (i) phenyl and naphthyl, and
 (ii) phenyl and naphthyl substituted by at least one substituent

- 1 selected from the group consisting of lower alkyl, lower alkoxy,
lower alkanoyl, acyloxy, hydroxy, carboxy, amino, halogen, nitro,
cyano, acylamino, mercapto, acylmercapto, halogeno-lower alkyl,
halogeno-lower alkoxy, lower alkylenedioxy, lower alkoxycarbonyl,
sulfo, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl
5 (c) (i) furyl, thienyl and pyridyl, and
(ii) furyl, thienyl and pyridyl substituted by at least one
substituent selected from the group consisting of lower alkyl,
lower alkoxy, lower alkanoyl, acyloxy, hydroxy, carboxy, amino,
halogen, nitro, cyano, acylamino, mercapto, acylmercapto,
halogeno-lower alkyl, halogeno-lower alkoxy, lower alkylene-
dioxy, lower alkoxycarbonyl, sulfo, sulfamoyl, lower alkyl-
10 aminosulfonyl and lower alkylsulfinyl;
and salts thereof.

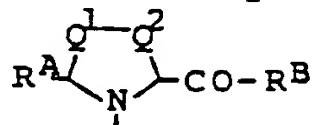
2. A compound of claim 1 wherein $-Q^1-Q^2-$ is $-\text{CH}_2\text{CH}_2-$,
 $-\text{SCH}_2-$ or $-\text{CH}_2\text{S}-$.

- 15 3. A compound of claim 1 wherein R^a is hydrogen, methyl,
ethyl, 1-methylethyl, propyl, 2-methylpropyl, butyl, 2,6-
dimethyl-5-heptenyl, cyclohexyl, S-acetyl-2-mercaptoethyl or
2-mercaptoethyl.

- 20 4. A compound of claim 1 wherein R^b is benzyl, 2-phenyl-
ethyl, 4-methylbenzyl, 4-methoxybenzyl, 2-hydroxybenzyl, 4-
hydroxybenzyl, 3-fluorobenzyl, 3-nitrobenzyl, 3-cyanobenzyl,
2-(4-methoxyphenyl)ethyl, 2-(2-hydroxyphenyl)ethyl, 2-(4-
hydroxyphenyl)ethyl, 2-(3-fluorophenyl)ethyl, 2-[3-(trifluoro-
methyl)phenyl]ethyl, 2-(3-nitrophenyl)ethyl, 2-(3-cyanophenyl)-
ethyl, 2-pyridylmethyl, 4-pyridylmethyl, 2-furylmethyl, 2-(2-
pyridyl)ethyl, 2-(4-pyridyl)ethyl, 2-(2-furyl)ethyl, phenyl,
25 4-methylphenyl, 2-chlorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl,
2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-nitrophenyl,
3-nitrophenyl, 4-nitrophenyl, 2-chloro-5-nitrophenyl, 4-dimethyl-

aminophenyl, 4-acetaminophenyl, 4-[(benzyloxycarbonyl)amino]phenyl, 2-carboxyphenyl, 4-carboxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-benzoxypyphenyl, 4-(benzyloxycarbonyloxy)phenyl, 3,4-dihydroxyphenyl, 5-chloro-2-hydroxyphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 2-hydroxy-3-methoxyphenyl, 2-hydroxy-4-methoxyphenyl, 4-hydroxy-3-methoxyphenyl, 3,4-methylenedioxyphenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 2-nitrosophenyl, 3-nitrosophenyl, 4-nitrosophenyl, 2-hydroxy-5-sulfamoylphenyl, 2-hydroxy-5-[(dipropylamino)sulfonyl]phenyl, 3-(methylsulfinyl)phenyl, 3-(difluoromethoxy)phenyl, 1-naphthyl, 2-furyl, 2-(5-methyl)furyl, 2-thienyl, 3-pyridyl or 4-pyridyl.

5. A compound of claim 1 wherein R^C is hydroxy, methoxy, ethoxy, butoxy, amino, hydroxyamino, succinimidomethoxy, 1-succinimidoethoxy, phthalimidomethoxy, 2-phthalimidoethoxy, pivaloyloxymethoxy, 1-pivaloyloxyethoxy, benzyloxy, phenoxy, benzyloxyamino or

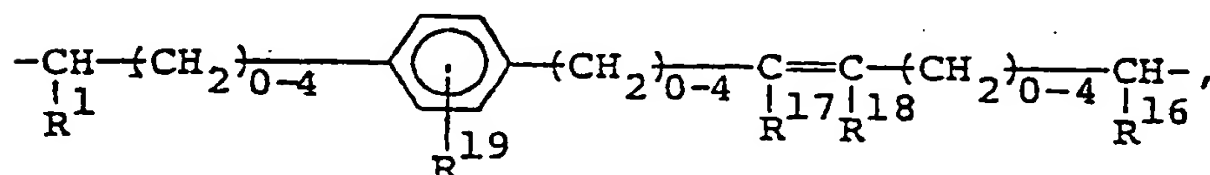
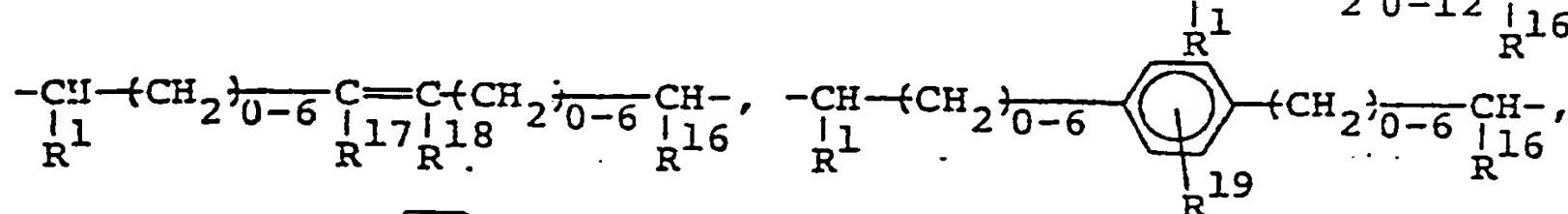


6. A compound of claim 1 wherein R^d is hydrogen, methyl, ethyl, propyl, 1-methylethyl, 2-methylpropyl, 4-methylpentyl, vinyl, allyl, 2-butenyl, 1,3-butanediethyl, 1-methylvinyl, hydroxymethyl, carboxymethyl, 2-carboxyethyl, cyclohexyl, cyclohexylmethyl, benzyl, 2-phenylethyl, 3-phenylbutyl, 2-(1-naphthyl)ethyl, 2-(4-chlorophenyl)ethyl, 2-(3,4-dichlorophenyl)ethyl, 4-methoxybenzyl, 2-(4-methoxyphenyl)ethyl, 4-hydroxybenzyl, 2-(4-hydroxyphenyl)ethyl, (2-pyridyl)methyl, (4-pyridyl)methyl, 2-(2-pyridyl)ethyl, 2-(4-pyridyl)ethyl, (4-imidazolyl)methyl, 3-indolylmethyl, 2-(methylthio)ethyl, 4-aminobutyl, 5-aminopentyl, 4-guanidinobutyl, 4-(aminomethyl)benzyl, phenoxy-methyl, (phenylthio)methyl, 1-amino-2-phenylethyl, 1-amino-3-methylbutyl phenyl, naphthyl, 4-methylphenyl, 2-chlorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 2-chloro-5-nitrophenyl, 4-dimethylaminophenyl, 4-acetaminophenyl, 2-carboxyphenyl, 4-carboxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-benzoxypyphenyl, 3,4-

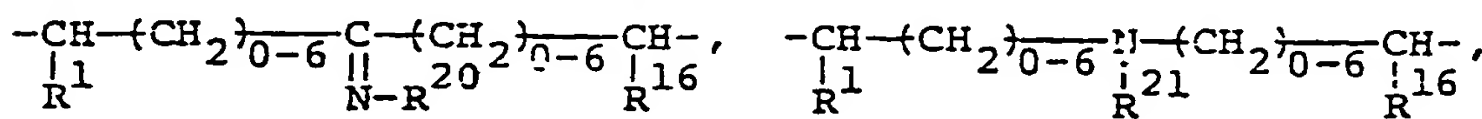
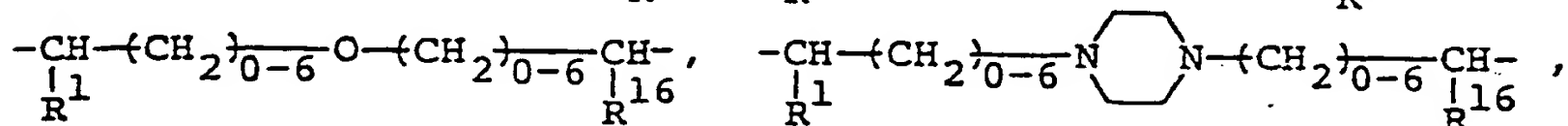
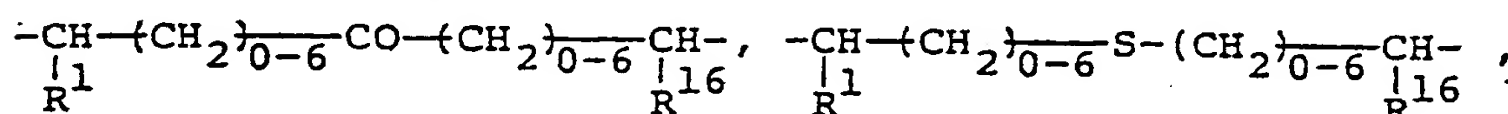
1 dihydroxyphenyl, 5-chloro-2-hydroxyphenyl, 2-methoxyphenyl,
4-methoxyphenyl, 3,4-dimethoxyphenyl, 3,4,5-trimethoxyphenyl,
2-hydroxy-3-methoxyphenyl, 2-hydroxy-5-sulfamoylphenyl, 3-
(methylsulfinyl)phenyl, 3-(difluoromethoxy)phenyl, 2-furyl, 2-(5-
methyl)furyl, 2-thienyl, 3-pyridyl or 4-pyridyl.

5

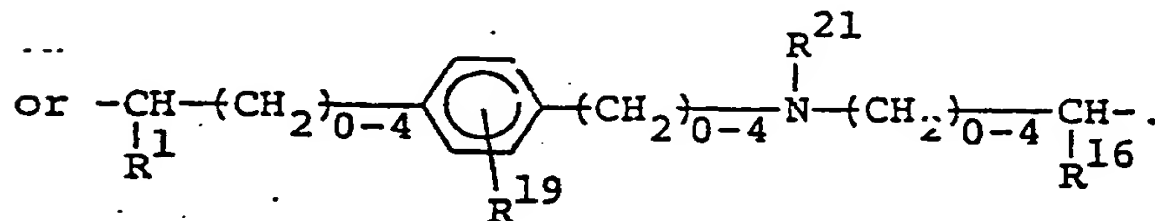
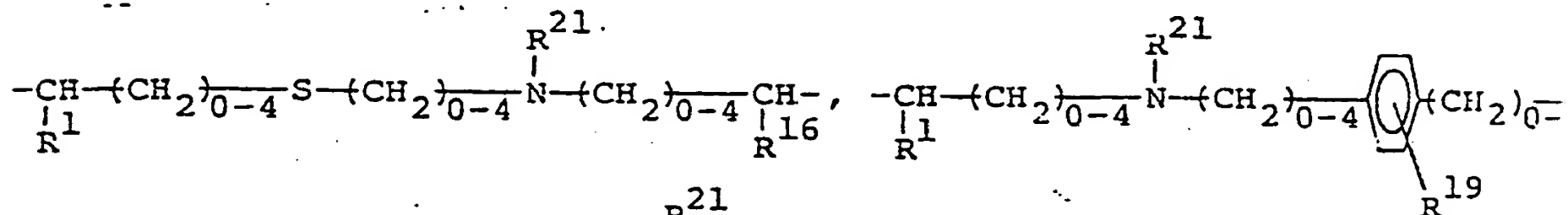
7. A compound of claim 1 wherein W is $-\text{CH}(\text{R}^1)-(\text{CH}_2)_{0-12}-\text{CH}(\text{R}^{16})-$,



0

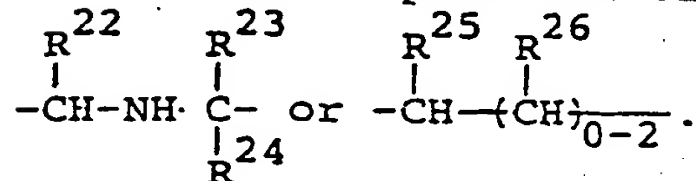


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10

8. A compound of claim 1, wherein R^A is R^B when W is



25

9. A compound of claim 4 which is (4R)-3-[8-(ethoxycarbonyl)octanoyl]-2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid.

1 10. A compound of claim 4 which is (4R,4'R)-3,3'-(nonanedioyl)bis[2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid methyl ester].

5 11. A compound according to claim 4 which is (4R)-3-(11-carboxyundecanoyl)-2-(3-cyanophenyl)-4-thiazolidinecarboxylic acid;

(4R,4'R)-3,3'-(~~decane~~edioyl)bis[2-(3-cyanophenyl)-4-thiazolidinecarboxylic acid];

(4R,4'R)-3,3'-(~~dodecane~~edioyl)bis[2-(3-cyanophenyl)-4-thiazolidinecarboxylic acid];

10 (4R)-3-(8-carboxyoctanoyl)-2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid;

(4R,4'R)-3,3'-(nonanedioyl)bis[2-(3-nitrophenyl)-4-thiazolidinecarboxylic acid];

(4R)-3-(7-carboxyheptanoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid.

15 12. A compound according to claim 4 which is (4R)-3-[[[(1-carboxy-3-phenylpropyl)amino]acetyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid;

(4R)-3-[[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]acetyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid.

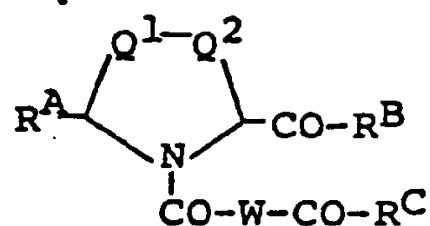
20 13. A compound according to claim 4 which is 1-[[[(1-carboxy-3-phenylpropyl)amino]acetyl]-2-(2-hydroxyphenyl)-5-pyrrolidinecarboxylic acid;

1-[[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]acetyl]-2-(2-hydroxyphenyl)-5-pyrrolidinecarboxylic acid.

25 14. A compound of claim 4 which is (4R)-3-[[[(1-carboxy-3-phenylpropyl)thio]acetyl]-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid.

15. A compound of claim 4 which is (4R)-3-(4-carboxybutanoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid.

1 16. A process for preparing a compound of the formula [I]



[I]

wherein

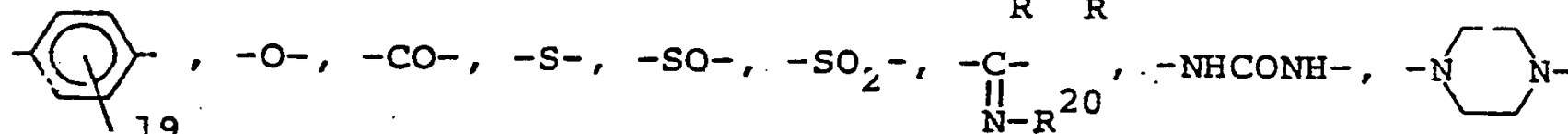
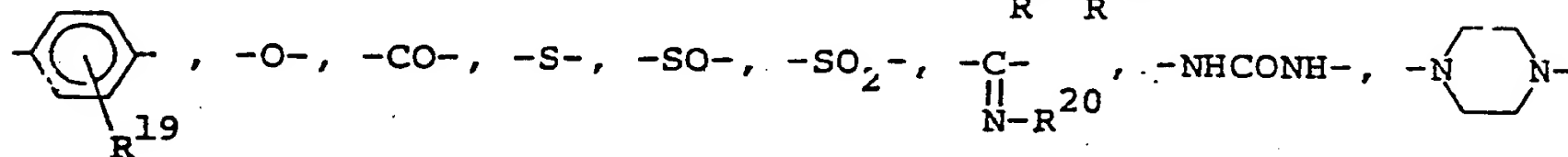
10 Q^1 and Q^2 each is methylene or sulfur, but Q^1 and Q^2 are not sulfur at the same time;

R^{A} is R^{a} or R^{b} ;

R^{B} and R^{C} each is R^{c} ;

15 W is $\left[\begin{array}{c} \text{R}^1 \\ | \\ \text{C} \\ | \\ \text{R}^2 \end{array} \right]_l \left[\begin{array}{c} \text{R}^3 \\ | \\ \text{C} \\ | \\ \text{R}^4 \end{array} \right]_m \text{X} \left[\begin{array}{c} \text{R}^5 \\ | \\ \text{C} \\ | \\ \text{R}^6 \end{array} \right]_n \left[\begin{array}{c} \text{R}^7 \\ | \\ \text{C} \\ | \\ \text{R}^8 \end{array} \right]_p \text{Y} \left[\begin{array}{c} \text{R}^9 \\ | \\ \text{C} \\ | \\ \text{R}^{10} \end{array} \right]_q \left[\begin{array}{c} \text{R}^{11} \\ | \\ \text{C} \\ | \\ \text{R}^{12} \end{array} \right]_r \text{Z} \left[\begin{array}{c} \text{R}^{13} \\ | \\ \text{C} \\ | \\ \text{R}^{14} \end{array} \right]_s \left[\begin{array}{c} \text{R}^{15} \\ | \\ \text{C} \\ | \\ \text{R}^{16} \end{array} \right]_t$, where

X, Y and Z each is single bond, $-\text{CH}_2-$, $-\text{C}=\text{C}-$, $-\text{C}\equiv\text{C}-$,



20

or $-\text{N}-$;
 $\begin{array}{c} | \\ \text{R}^{21} \end{array}$

l, m, n, p, q, r, s and t each is 0, 1, 2 or 3;
 $\text{R}^1, \text{R}^2, \text{R}^3, \dots, \text{R}^{20}$ and R^{21} each is R^{d} ;

25 R^{A} is R^{b} when W is $-\text{CH}-\text{NH}-\text{C}-$ or $-\text{CH}-\text{CH}-$, wherein $\text{R}^{22}, \text{R}^{23}, \text{R}^{24}, \text{R}^{25}$ and R^{26} each is R^{d} .

1 R^a is selected from the group consisting of
(i) hydrogen, lower alkyl and lower alkenyl, and
(ii) lower alkyl and lower alkenyl substituted by at least one
substituent selected from the group consisting of lower alkyl,
lower alkenyl, hydroxy, lower alkoxy, halogeno-lower alkoxy,
5 acyloxy, halogen, nitro, cyano, amino, lower alkylamino, di-
alkylamino, acylamino, mercapto, acylmercapto, lower alkylthio,
carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl,
sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

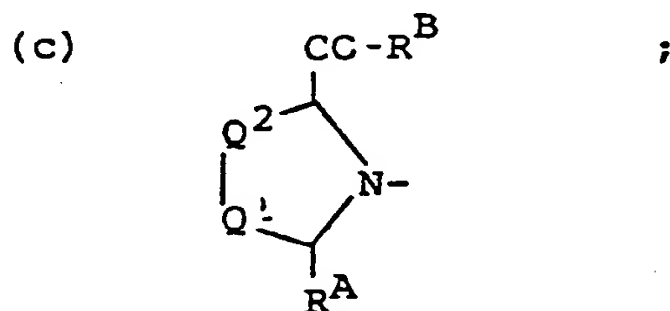
R^b is selected from the group consisting of
(a) (i) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl, and
10 (ii) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl
substituted by at least one substituent selected from the group
consisting of lower alkyl, lower alkenyl, halogeno-lower alkyl,
hydroxy, lower alkoxy, halogeno-lower alkoxy, acyloxy, halogen,
nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino,
mercapto, acylmercapto, lower alkylthio, carboxy, lower alkoxy-
15 carbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower
alkylaminosulfonyl and lower alkylsulfinyl, and
(iii) carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl, aryloxy-
carbonyl and heteroaryloxycarbonyl;

(b) (i) phenyl and naphthyl, and
(ii) phenyl and naphthyl substituted by at least one substituent
selected from the group consisting of lower alkyl, lower alkenyl,
20 halogeno-lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy,
aralkyloxy, aryloxy, acyloxy, halogen, nitro, cyano, amino,
lower alkylamino, dialkylamino, acylamino, mercapto, acylmercapto,
lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl,
aryloxycarbonyl, sulfamoyl, lower alkylaminosulfonyl and lower
alkylsulfinyl;

25 (c) (i) furyl, thienyl and pyridyl, and
(ii) furyl, thienyl and pyridyl substituted by at least one
substituent selected from the group consisting of lower alkyl,

- 1 lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy,
 halogeno-lower alkoxy aralkyloxy, aryloxy, acyloxy, halogen, nitr
 cyano, amino, lower alkylamino, dialkylamino, acylamino, mercapto
 acylmercapto, lower alkylthio, carboxy, lower alkoxycarbonyl,
 aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl, lower alkyl-
 5 aminosulfonyl and lower alkylsulfinyl;

- R^C is selected from the group consisting of
 (a) (i) hydroxy, lower alkoxy and amino, and
 (ii) lower alkoxy and amino substituted by at least one substitue
 selected from the group consisting of lower alkyl, aralkyl,
 heteroaralkyl, aralkenyl, heteroaralkenyl, hydroxy, lower alkoxy,
 10 aralkyloxy, heteroaralkyloxy, aryloxy, heteroaryloxy, acyloxy,
 aryl, heteroaryl, substituted aralkyl and substituted aryl
 wherein the substituent is lower alkyl, lower alkoxy, halogen
 or amino;
 (b) (i) aryloxy and heteroaryloxy, and
 (ii) aryloxy and heteroaryloxy substituted by at least one
 15 substituent selected from the group consisting of lower alkyl,
 hydroxy, lower alkoxy, halogen and amino, and



- 20 R^d is selected from the group consisting of
 (a) (i) hydrogen, lower alkyl, lower alkenyl, aralkyl, hetero-
 aralkyl, alkanoyl, arylalkanoyl, heteroarylalkanoyl, hydroxy,
 carboxy, amino, mercapto and sulfo, and
 (ii) lower alkyl, lower alkenyl, aralkyl, heteroaralkyl,
 alkanoyl arylalkanoyl, heteroarylalkanoyl, hydroxy, carboxy,
 25 amino, mercapto and sulfo substituted by at least one
 substituent selected from the group consisting of lower alkyl,
 lower alkenyl, lower alkoxy, lower alkanoyl, aryl, heteroaryl,
 acyloxy, aroyl, hydroxy, carboxy, amino, guanidino, mercapto,

1 acylamino, acylmercapto, lower alkoxycarbonyl, sulfo, halogen,
nitro, cyano, sulfamoyl, lower alkylaminosulfonyl, lower alkyl-
thio and lower alkylsulfinyl;

(b)(i) phenyl and naphthyl, and

5 (ii) phenyl and naphthyl substituted by at least one substituent
selected from the group consisting of lower alkyl, lower alkoxy,
lower alkanoyl, acyloxy, hydroxy, carboxy, amino, halogen, nitro,
cyano, acylamino, mercapto, acylmercapto, halogeno-lower alkyl,
halogeno-lower alkoxy, lower alkylenedioxy, lower alkoxycarbonyl,
sulfo, sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

(c)(i) furyl, thienyl and pyridyl, and

10 (ii) furyl, thienyl and pyridyl substituted by at least one
substituent selected from the group consisting of lower alkyl,
lower alkoxy, lower alkanoyl, acyloxy, hydroxy, carboxy, amino,
halogen, nitro, cyano, acylamino, mercapto, acylmercapto,
halogeno-lower alkyl, halogeno-lower alkoxy, lower alkylene-
dioxy, lower alkoxycarbonyl, sulfo, sulfamoyl, lower alkyl-
aminosulfonyl and lower alkylsulfinyl;

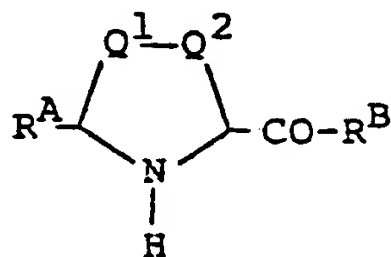
15

and salts thereof

which comprises

(i) reacting a compound of the formula [II]

20



[II]

25

wherein R^A and R^B may include suitable protection of any reactive
groups with the reactive derivative of a carboxylic acid of the
formula [III] (e.g., acyl halide, acid anhydride, mixed anhydride,
active ester, etc.)

1 of any reactive groups, followed by removal of protective
groups, if necessary, to yield a compound of the formula [I];

(iii) reacting a compound of the formula [II] with the
reactive derivative of carboxylic acid of the formula [VII]

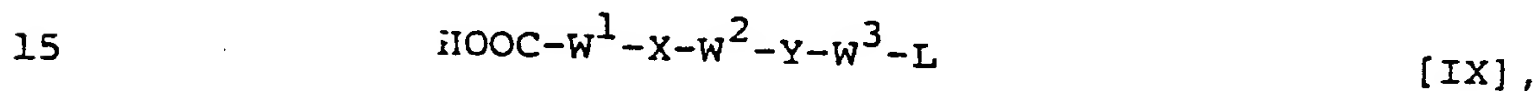


and then with a compound of the formula [VIII]



10 by the same method as (ii) above to yield a compound of the
formula [I];

(iv) reacting a compound of the formula [II] with the
reactive derivative of carboxylic acid of the formula [IX]



and then with a compound of the formula [X]

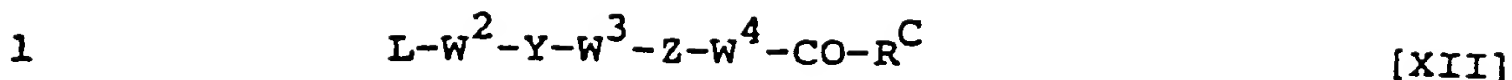


20 by the same method as (ii) above to yield a compound of
the formula [I];

(v) reacting a compound of the formula [II] with the
reactive derivative of carboxylic acid of the formula [XI]



25 and then with a compound of the formula [XII]

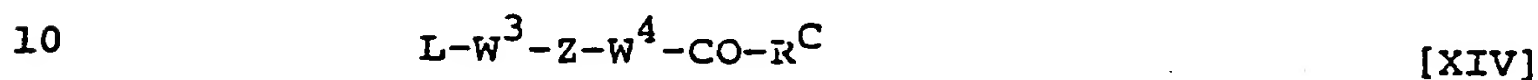


by the same method as (ii) above to yield a compound of the formula [I];

- 5 (vi) reacting a compound of the formula [II] with the reactive derivative of carboxylic acid of the formula [XIII]

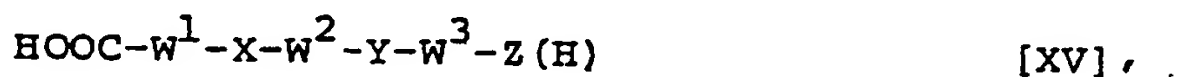


and then with a compound of the formula [XIV]



by the same method as (ii) above to yield a compound of the formula [I], or

- 15 (vii) reacting a compound of the formula [II] with the reactive derivative of carboxylic acid of the formula [XV]



and then with a compound of the formula [XVI]

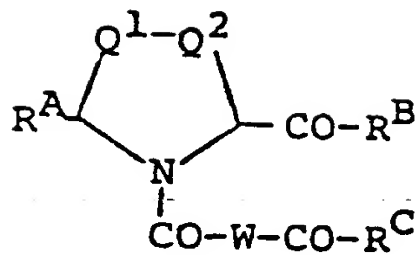


by the same method as (ii) above to yield a compound of the formula [I];

furthermore converting R^B , R^C , X, Y and Z to other functional groups by the general methods, if desired, to obtain a desired compound of the formula [I].

25

17. A composition comprising a compound of the formula [I]



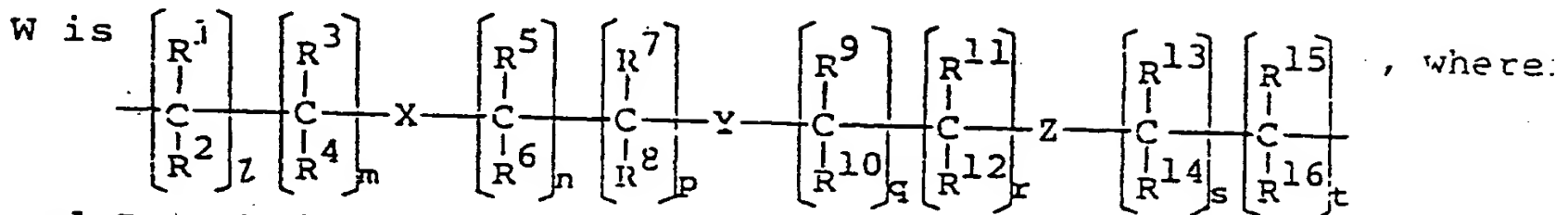
[I]

wherein

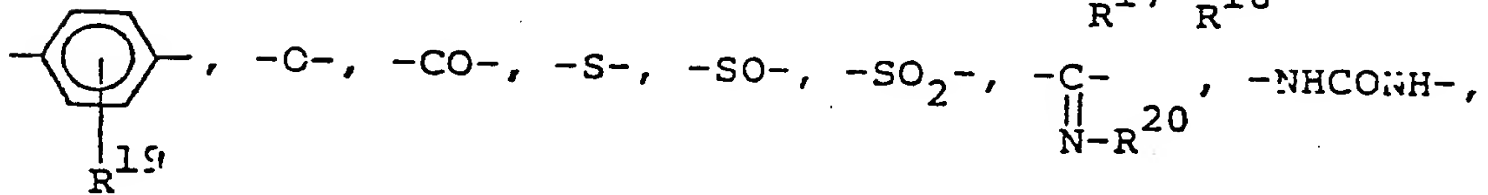
Q^1 and Q^2 each is methylene or sulfur, but Q^1 and Q^2 are not sulfur at the same time;

R^{A} is R^{a} or R^{b} ;

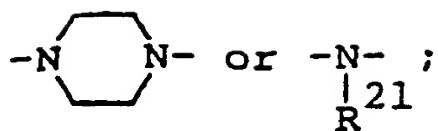
R^{B} and R^{C} each is R^{c} ;



X, Y and Z each is single bond, $-\text{CH}_2-$, $-\text{C}=\text{C}-$, $-\text{C}\equiv\text{C}-$,



1



l, m, n, p, q, r, s and t each is 0, 1, 2 or 3;
 $R^1, R^2, R^3, \dots, R^{20}$ and R^{21} each is R^d ;

5

R^a is selected from the group consisting of
 (i) hydrogen, lower alkyl and lower alkenyl, and
 (ii) lower alkyl and lower alkenyl substituted by at least
 one substituent selected from the group consisting of lower
 alkyl, lower alkenyl, hydroxy, lower alkoxy, halogeno-lower
 alkoxy, acyloxy, halogen, nitro, cyano, amino, lower alkyl-
 amino, dialkylamino, acylamino, mercapto, acylmercapto,
 lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxy-
 carbonyl, aryloxy carbonyl, sulfamoyl, lower alkylamino-
 sulfonyl and lower alkylsulfinyl;

10

15

20

R^b is selected from the group consisting of
 (a) (i) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl,
 (ii) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl
 substituted by at least one substituent selected from the
 group consisting of lower alkyl, lower alkenyl, halogeno-
 lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy,
 acyloxy, halogen, nitro, cyano, amino, lower alkylamino,
 dialkylamino, acylamino, mercapto, acylmercapto, lower
 alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl,
 aryloxy carbonyl, sulfamoyl, lower alkylaminosulfonyl and
 lower alkylsulfinyl, and
 (iii) carboxy, lower alkoxycarbonyl, aralkyloxycarbonyl,
 aryloxy carbonyl and heteroaryloxy carbonyl;

25

(b) (i) phenyl and naphthyl, and
 (ii) phenyl and naphthyl substituted by at least one
 substituent selected from the group consisting of lower
 alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower
 alkoxy, halogeno-lower alkoxy, aralkyloxy, aryloxy, acyloxy,
 halogen, nitro, cyano, amino, lower alkylamino, dialkylamino,

- 1 acylamino, mercapto, acylmercapto, lower alkylthio, carboxy,
lower alkoxy carbonyl, aralkyloxy carbonyl, aryloxy carbonyl,
sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;
(c) (i) furyl, thienyl and pyridyl, and
(ii) furyl, thienyl and pyridyl substituted by at least one
5 substituent selected from the group consisting of lower
alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower
alkoxy, halogeno-lower alkoxy, aralkyloxy, aryloxy, acyloxy,
halogen, nitro, cyano, amino, lower alkylamino, dialkylamino,
acylamino, mercapto, acylmercapto, lower alkylthio, carboxy,
lower alkoxy carbonyl, aralkyloxy carbonyl, aryloxy carbonyl,
sulfamoyl, lower alkylaminosulfonyl and lower alkylsulfinyl;

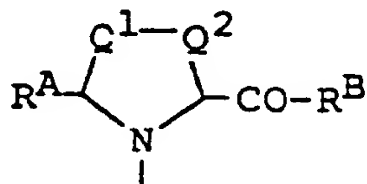
10

R^C is selected from the group consisting of

- (a) (i) hydroxy, lower alkoxy and amino, and
(ii) lower alkoxy and amino substituted by at least one
substituent selected from the group consisting of lower
15 alkyl, aralkyl, heteroaralkyl, aralkenyl, heteroaralkenyl,
hydroxy, lower alkoxy, aralkyloxy, heteroaralkyloxy, aryloxy,
heteroaryloxy, acyloxy, aryl, heteroaryl, substituted
aralkyl and substituted aryl wherein the substituent is
lower alkyl, lower alkoxy, halogen, or amino;

- (b) (i) aryloxy and heteroaryloxy, and
(ii) aryloxy and heteroaryloxy substituted by at least one
20 substituent selected from the group consisting of lower
alkyl, hydroxy, lower alkoxy, halogen and amino, and

(c)



R^d is selected from the group consisting of

- 25 (a) (i) hydrogen, lower alkyl, lower alkenyl, aralkyl,
heteroaralkyl, alkanoyl, arylalkanoyl, heteroarylalkanoyl,
hydroxy, carboxy, amino, mercapto and sulfo, and

- 1 (a)(ii) lower alkyl, lower alkenyl, aralkyl, heteroaralkyl,
alkanoyl, arylalkanoyl, heteroarylalkanoyl, hydroxy, carboxy,
amino, mercapto and sulfo substituted by at least one
substituent selected from the group consisting of lower
alkyl, lower alkenyl, lower alkoxy, lower alkanoyl, aryl,
heteroaryl, acyloxy, aroyl, hydroxy, carboxy, amino, guanidino,
5 mercapto, acylamino, acylmercapto, lower alkoxycarbonyl,
sulfo, halogen, nitro, cyano, sulfamoyl, lower alkylamino-
sulfonyl, lower alkylthio and lower alkylsulfinyl;

(b)(i) phenyl and naphthyl, and
(ii) phenyl and naphthyl substituted by at least one
substituent selected from the group consisting of lower alkyl,
10 lower alkoxy, lower alkanoyl, acyloxy, hydroxy, carboxy,
amino, halogen, nitro, cyano, acylamino, mercapto, acyl-
mercapto, halogeno-lower alkyl, halogeno-lower alkoxy,
lower alkylenedioxy, lower alkoxycarbonyl, sulfo, sulfamoyl,
lower alkylaminosulfonyl and lower alkylsulfinyl;

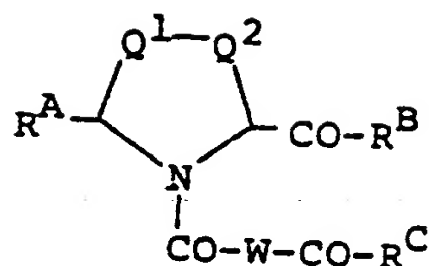
(c)(i) furyl, thienyl and pyridyl, and
15 (ii) furyl, thienyl and pyridyl substituted by at least
one substituent selected from the group consisting of
lower alkyl, lower alkoxy, lower alkanoyl, acyloxy, hydroxy,
carboxy, amino, halogen, nitro, cyano, acylamino, mercapto,
acylmercapto, halogeno-lower alkyl, halogeno-lower alkoxy,
lower alkylenedioxy, lower alkoxycarbonyl; sulfo, sulfamoyl,
20 lower alkylaminosulfonyl and lower alkylsulfinyl;

or salts thereof in an amount sufficient to prevent or
relieve diabetes mellitus associated complications consisting
of cataracts, neuropathy, nephropathy and retinopathy, and
pharmaceutically acceptable excipient(s).

- 25 18. A composition comprising a compound of the formula [I]

1

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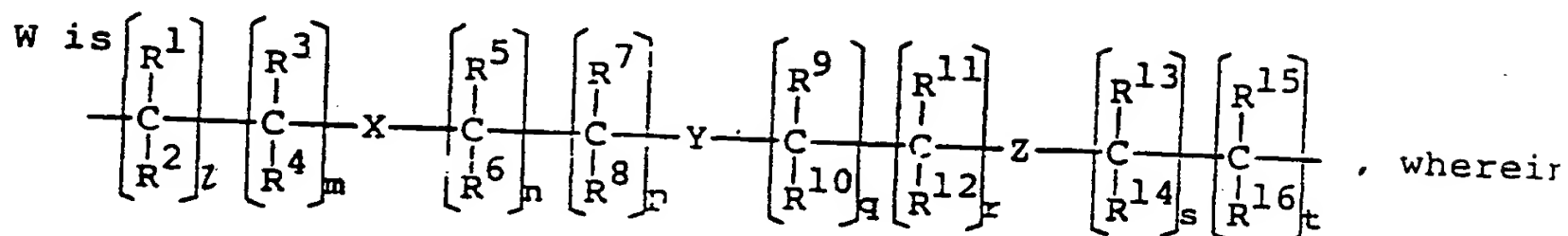
[I]

10 wherein

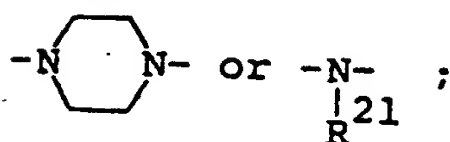
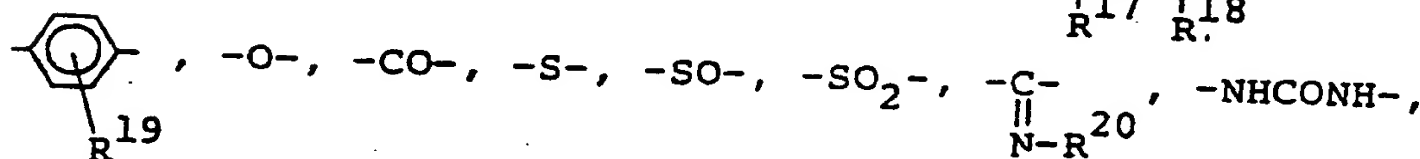
Q^1 and Q^2 each is methylene or sulfur, but Q^1 and Q^2 are not sulfur at the same time;

R^A is R^a or R^b ;

15 R^B and R^C each is R^c ;



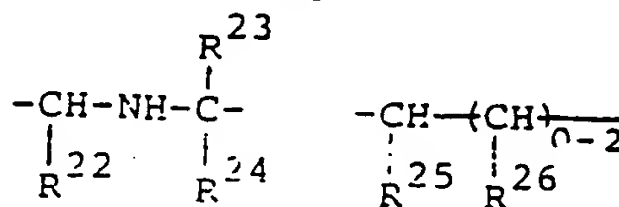
20 X, Y and Z each is single bond, $-\text{CH}_2-$, $-\text{C}=\text{C}-$, $-\text{C}\equiv\text{C}-$,
 R^{17} R^{18}



25 z, m, n, p, q, r, s and t each is 0, 1, 2 or 3;
 $\text{R}^1, \text{R}^2, \text{R}^3, \dots, \text{R}^{20}$ and R^{21} each is R^d ;

R^A is R^b when W is

or

, wherein R^{22} ,

1 R^{23} , R^{24} , R^{25} and R^{26} each is R^d ;

5 R^a is selected from the group consisting of
(i) hydrogen, lower alkyl and lower alkenyl, and
(ii) lower alkyl and lower alkenyl substituted by at least
one substituent selected from the group consisting of lower
alkyl, lower alkenyl, hydroxy, lower alkoxy, halogeno-lower
alkoxy, acyloxy, halogen, nitro, cyano, amino, lower alkyl-
amino, dialkylamino, acylamino, mercapto, acylmercapto,
lower alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxy-
carbonyl, aryloxy-carbonyl, sulfamoyl, lower alkylamino-
sulfonyl and lower alkylsulfinyl;

10

R^b is selected from the group consisting of
(a) (i) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl,
(ii) aralkyl, heteroaralkyl, aralkenyl and heteroaralkenyl
substituted by at least one substituent selected from the
group consisting of lower alkyl, lower alkenyl, halogeno-
lower alkyl, hydroxy, lower alkoxy, halogeno-lower alkoxy,
15 acyloxy, halogen, nitro, cyano, amino, lower alkylamino,
dialkylamino, acylamino, mercapto, acylmercapto, lower
alkylthio, carboxy, lower alkoxycarbonyl, aralkyloxy-
carbonyl, aryloxy-carbonyl, sulfamoyl, lower alkylamino-
sulfonyl and lower alkylsulfinyl, and
(iii) carboxy, lower alkoxycarbonyl, aralkyloxy-carbonyl,
20 aryloxy-carbonyl and heteroaryloxy-carbonyl;

20

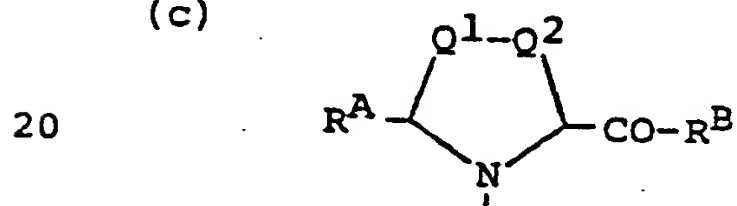
(b) (i) phenyl and naphthyl, and
(ii) phenyl and naphthyl substituted by at least one
substituent selected from the group consisting of lower
alkyl, lower alkenyl, halogeno-lower alkyl, hydroxy, lower
alkoxy, halogeno-lower alkoxy, aralkyloxy, aryloxy, acyloxy,
halogen, nitro, cyano, amino, lower alkylamino, dialkylamino,
25 acylamino, mercapto, acylmercapto, lower alkylthio, carboxy,
lower alkoxycarbonyl, aralkyloxy-carbonyl, aryloxy-carbonyl,
sulfamoyl, lower alkylsulfonyl and lower alkylsulfinyl;

25

- 1 (c) (i) furyl, thienyl and pyridyl, and
 (ii) furyl, thienyl and pyridyl substituted by at least one
 substituent selected from the group consisting of lower alkyl,
 lower alkenyl, halogeno-lower alkyl, hydroxy, lower alkoxy,
 halogeno-lower alkoxy, aralkyloxy, aryloxy, acyloxy, halogen,
 5 nitro, cyano, amino, lower alkylamino, dialkylamino, acylamino,
 mercapto, acylmercapto, lower alkylthio, carboxy, lower
 alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, sulfamoyl,
 lower alkylsulfonyl, and lower alkylsulfinyl;

- R^C is selected from the group consisting of
 (a) (i) hydroxy, lower alkoxy and amino, and
 10 (ii) lower alkoxy and amino substituted by at least one
 substituent selected from the group consisting of lower
 alkyl, aralkyl, heteroaralkyl, aralkenyl, heteroaralkenyl,
 hydroxy, lower alkoxy, aralkyloxy, heteroaralkyloxy, aryloxy,
 heteroaryloxy, acyloxy, aryl, heteroaryl, substituted
 aralkyl and substituted aryl wherein the substituent is
 15 lower alkyl, lower alkoxy, halogen or amino;
 (b) (i) aryloxy and heteroaryloxy, and
 (ii) aryloxy and heteroaryloxy substituted by at least one
 substituent selected from the group consisting of lower alkyl,
 hydroxy, lower alkoxy, halogen and amino, and

(c)



- R^d is selected from the group consisting of
 (a) (i) hydrogen, lower alkyl, lower alkenyl, aralkyl,
 heteroaralkyl, alkanoyl, arylalkanoyl, heteroarylalkanoyl,
 hydroxy, carboxy, amino, mercapto and sulfo, and
 25 (ii) lower alkyl, lower alkenyl, aralkyl, heteroaralkyl,
 alkanoyl, arylalkanoyl, heteroarylalkanoyl, hydroxy,
 carboxy, amino, mercapto and sulfo substituted by at least

- 1 one substituent selected from the group consisting of lower
alkyl, lower alkenyl, lower alkoxy, lower alkanoyl, aryl,
heteroaryl, acyloxy, aroyl, hydroxy, carboxy, amino,
guanidino, mercapto, acylamino, acylmercapto, lower alkoxy-
5 carbonyl, sulfo, halogen, nitro, cyano, sulfamoyl, lower
alkylaminosulfonyl, lower alkylthio and lower alkylsulfinyl;
(b) (i) phenyl and naphthyl, and
(ii) phenyl and naphthyl substituted by at least one
substituent selected from the group consisting of lower
alkyl, lower alkoxy, lower alkanoyl, acyloxy, hydroxy,
carboxy, amino, halogen, nitro, cyano, acylamino, mercapto,
10 acylmercapto, halogeno-lower alkyl, halogeno-lower alkoxy,
lower alkylenedioxy, lower alkoxycarbonyl, sulfo, sulfamoyl,
lower alkylaminosulfonyl and lower alkylsulfinyl;
(c) (i) furyl, thienyl and pyridyl, and
(ii) furyl, thienyl and pyridyl substituted by at least
one substituent selected from the group consisting of
lower alkyl, lower alkoxy, lower alkanoyl, acyloxy,
15 hydroxy, carboxy, amino, halogen, nitro, cyano, acylamino,
mercapto, acylmercapto, halogeno-lower alkyl, halogeno-
lower alkoxy, lower alkylenedioxy, lower alkoxycarbonyl,
sulfo, sulfamoyl, lower alkylaminosulfonyl and lower
alkylsulfinyl;
20 or salts thereof in an amount sufficient to reduce blood
pressure and pharmaceutically acceptable excipient(s).
19. A compound according to claim 1 to 16 for use in a
method for therapy or prophylaxis.
20. Use of a compound according to claim 1 to 16 in a
process for producing pharmaceutical compositions.
- 25



European Patent
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EUROPEAN SEARCH REPORT

0031104

Application number

EP 80 10 7869

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
*	<p>US - A - 4 154 937 (D.W. CUSHMAN et al.)</p> <p>* Columns 1-2 *</p> <p>--</p>	<p>1-3, 5, 6, 7, 16</p>	<p>C 07 D 277/06 207/16 A 61 K 31/425 31/40</p>
*	<p>GB - A - 2 000 508 (YOSHITOMI PHARM. LTD.)</p> <p>* Pages 1-2 *</p> <p>--</p>	<p>1-5, 7, 16</p>	
	<p>FR - A - 2 407 204 (SANDOZ S.A.)</p> <p>* "Revendications" *</p> <p>--</p>	<p>1-5</p>	<p>TECHNICAL FIELDS SEARCHED (Int. Cl.)</p>
	<p>FR - A - 2 412 537 (SCIENCE UNION ET CIE)</p> <p>* "Revendications" *</p> <p>--</p>	<p>1, 2</p>	<p>C 07 D 277/06 277/16</p>
	<p>FR - A - 2 340 933 (E.R. SQUIBB AND SONS)</p> <p>* "Revendications" *</p> <p>--</p>	<p>1-3, 5-7</p>	<p>CATEGORY OF CITED DOCUMENTS</p> <p>X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons</p>
	<p>FR - A - 2 340 932 (E.R. SQUIBB AND SONS)</p> <p>* "Revendications" *</p> <p>--</p>	<p>1-3, 5-7</p>	
	<p>FR - A - 2 023 741 (EPROVA AG)</p> <p>* "Revendications" *</p> <p>--</p>	<p>1</p>	<p>&: member of the same patent family. corresponding document</p>
P	<p>EP - A - 0 007 477 (DAINIPPON PHARM)</p> <p>* "Revendications" *</p>	<p>1-5</p>	
<p>The present search report has been drawn up for all claims</p>			
Place of search		Date of completion of the search	Examiner
The Hague		09-03-1981	BRIGHENTI



European Patent
Office

EUROPEAN SEARCH REPORT

0031104

Application number

EP 80 10 7869
-2-

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
P	<u>FR - A - 2 445 324</u> (SANTEN PHARM) *"Revendications"* --	1-5	TECHNICAL FIELDS SEARCHED (Int. Cl. ³)
P	<u>FR - A - 2 440 365</u> (SANTEN PHARM) *"Revendications"* --	1-5	
P	<u>FR - A - 2 434 150</u> (YOSHITOMI PHARM.) *"Revendications"* ----	1-5	

